```
 NEWS X25      X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:01:18 ON 02 JAN 2007

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 13:01:31 ON 02 JAN 2007
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     1 JAN 2007  HIGHEST RN 916582-62-2
DICTIONARY FILE UPDATES:    1 JAN 2007  HIGHEST RN 916582-62-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

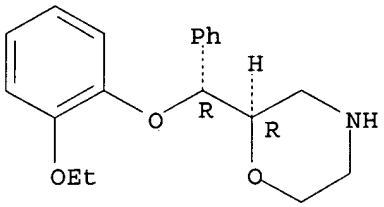
http://www.cas.org/ONLINE/UG/regprops.html

=> s reboxetine
L1           10 REBOXETINE

=> d 1-10

L1   ANSWER 1 OF 10  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   869898-89-5  REGISTRY
ED   Entered STN:  14 Dec 2005
CN   Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, hydrobromide,
     (2R)-rel- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Reboxetine hydrobromide
FS   STEREOSEARCH
MF   C19 H23 N O3 . Br H
SR   CA
LC   STN Files:   CA, CAPLUS
CRN  (71620-89-8)

Relative stereochemistry.
```



● HBr

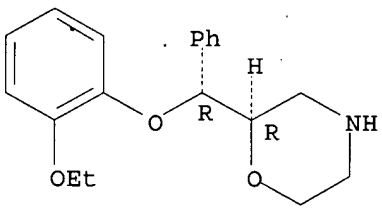
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 868161-64-2 REGISTRY
ED Entered STN: 16 Nov 2005
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)-rel-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Reboxetine fumarate
FS STEREOSEARCH
MF C19 H23 N O3 . C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 71620-89-8
CMF C19 H23 N O3

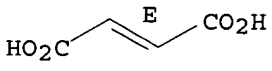
Relative stereochemistry.



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

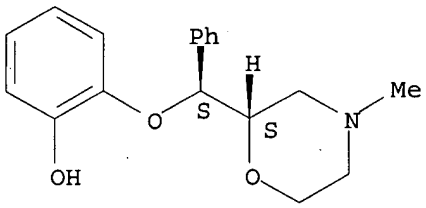


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 847996-52-5 REGISTRY
ED Entered STN: 06 Apr 2005

CN Phenol, 2-[(R)-[(2R)-4-methyl-2-morpholinyl]phenylmethoxy]-, rel- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-N-Methyldesethylreboxetine
FS STEREOSEARCH
MF C18 H21 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Relative stereochemistry.

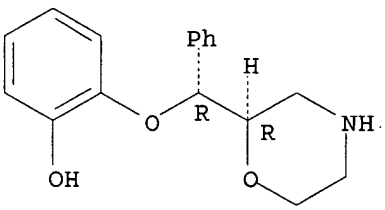


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 351330-75-1 REGISTRY
ED Entered STN: 14 Aug 2001
CN Phenol, 2-[(R)-(2R)-2-morpholinylphenylmethoxy]-, rel- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Relative stereochemistry.



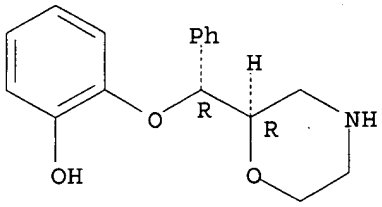
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 252570-32-4 REGISTRY
ED Entered STN: 10 Jan 2000
CN Phenol, 2-[(R)-(2R)-2-morpholinylphenylmethoxy]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2R,3R)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA

LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER

Absolute stereochemistry.

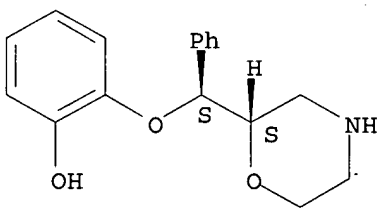


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 252570-31-3 REGISTRY
ED Entered STN: 10 Jan 2000
CN Phenol, 2-[(S)-(2S)-2-morpholinylphenylmethoxy]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-(2S,3S)-2-[2-Morpholinylphenylmethoxy]phenol
CN (2S,3S)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Absolute stereochemistry.

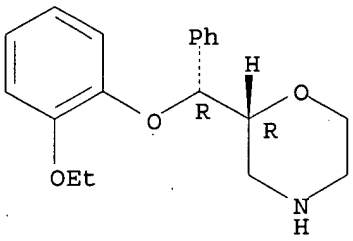


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 105017-38-7 REGISTRY
ED Entered STN: 01 Nov 1986
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, [R-(R*,R*)]-
OTHER NAMES:
CN (R,R)-(-)-Reboxetine
FS STEREOSEARCH
MF C19 H23 N O3
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

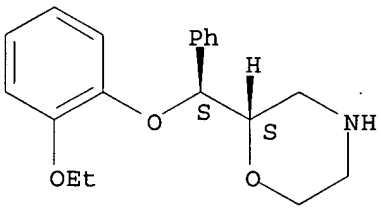


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 98819-76-2 REGISTRY
ED Entered STN: 02 Nov 1985
CN Morpholine, 2-[(S)-(2-ethoxyphenoxy)phenylmethyl]-, (2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, [S-(R*,R*)]-
OTHER NAMES:
CN (S,S)-(+)-Reboxetine
FS STEREOSEARCH
MF C19 H23 N O3
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

32 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
32 REFERENCES IN FILE CAPLUS (1907 TO DATE)

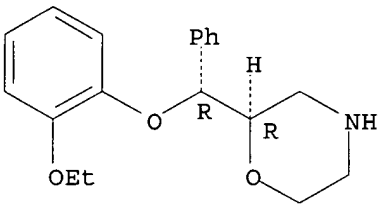
L1 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 98769-84-7 REGISTRY
ED Entered STN: 26 Oct 1985
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)-rel-, methanesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, (R*,R*)-(±)-, methanesulfonate
OTHER NAMES:

CN Davedax
CN Edronax
CN FCE 20124
CN PNU 155905E
CN PNU 155950E
CN Reboxetine mesylate
FS STEREOSEARCH
DR 98769-82-5, 141425-90-3
MF C19 H23 N O3 . C H4 O3 S
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

CM 1

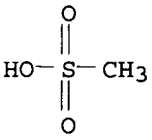
CRN 71620-89-8
CMF C19 H23 N O3

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

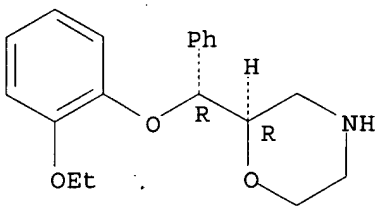
L1 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2007 ACS on STN
RN 71620-89-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)-rel- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Reboxetine
CN Reboxitine
FS STEREOSEARCH
DR 98769-81-4, 98769-83-6, 71621-36-8
MF C19 H23 N O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE,

MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: WHO

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

382 REFERENCES IN FILE CA (1907 TO DATE)
9 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
384 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
NEWS X25      X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
specific topic.

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  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 19:01:56 ON 23 DEC 2006

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 19:02:05 ON 23 DEC 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   22 DEC 2006  HIGHEST RN 916305-68-5
DICTIONARY FILE UPDATES:  22 DEC 2006  HIGHEST RN 916305-68-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s reboxetin
             0 REBOXETIN
L1           0 REBOXETIN

=> s reboxetine
L2          10 REBOXETINE

=> d 1-10

L2   ANSWER 1 OF 10  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   869898-89-5  REGISTRY
ED   Entered STN:  14 Dec 2005.
CN   Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, hydrobromide,
     (2R)-rel- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Reboxetine hydrobromide
FS   STEREOSEARCH
MF   C19 H23 N O3 . Br H
SR   CA
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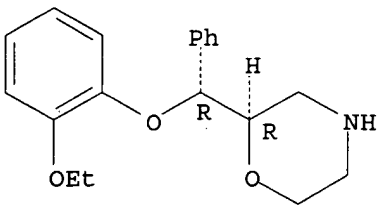
LC STN Files: CA, CAPLUS
CRN (71620-89-8)

Relative stereochemistry.



● HBr

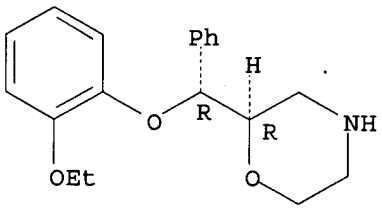
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 868161-64-2 REGISTRY
ED Entered STN: 16 Nov 2005
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)-rel-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Reboxetine fumarate
FS STEREOSEARCH
MF C19 H23 N O3 . C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 71620-89-8
CMF C19 H23 N O3

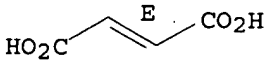
Relative stereochemistry.



CM 2

CRN 110-17-8
CMF C4 H4 O4

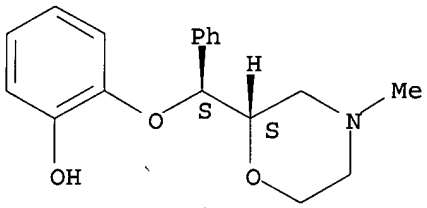
Double bond geometry as shown.



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 847996-52-5 REGISTRY
ED Entered STN: 06 Apr 2005
CN Phenol, 2-[(R)-[(2R)-4-methyl-2-morpholinyl]phenylmethoxy]-, rel- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-N-Methyldesethylreboxetine
FS STEREOSEARCH
MF C18 H21 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Relative stereochemistry.

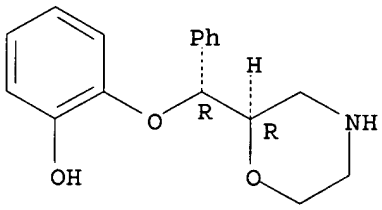


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 351330-75-1 REGISTRY
ED Entered STN: 14 Aug 2001
CN Phenol, 2-[(R)-(2R)-2-morpholinylphenylmethoxy]-, rel- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (±)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Relative stereochemistry.



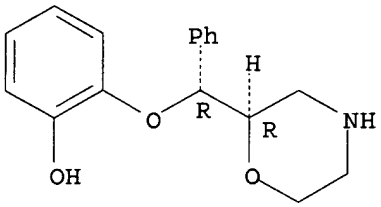
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 252570-32-4 REGISTRY
ED Entered STN: 10 Jan 2000
CN Phenol, 2-[(R)-(2R)-2-morpholinylphenylmethoxy]- (9CI) (CA INDEX NAME)
OTHER NAMES:

CN (2R,3R)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER

Absolute stereochemistry.

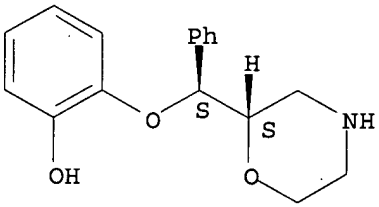


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 252570-31-3 REGISTRY
ED Entered STN: 10 Jan 2000
CN Phenol, 2-[(S)-(2S)-2-morpholinylphenylmethoxy]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (+)-(2S,3S)-2-[2-Morpholinylphenylmethoxy]phenol
CN (2S,3S)-Desethylreboxetine
FS STEREOSEARCH
MF C17 H19 N O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL

Absolute stereochemistry.



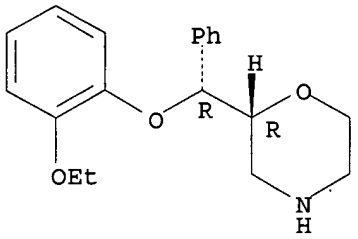
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2006 ACS on STN
RN 105017-38-7 REGISTRY
ED Entered STN: 01 Nov 1986
CN Morpholine, 2-[(R)-(2-ethoxyphenoxy)phenylmethyl]-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Morpholine, 2-[(2-ethoxyphenoxy)phenylmethyl]-, [R-(R*,R*)]-
OTHER NAMES:
CN (R,R)-(-)-Reboxetine
FS STEREOSEARCH
MF C19 H23 N O3
CI COM

SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



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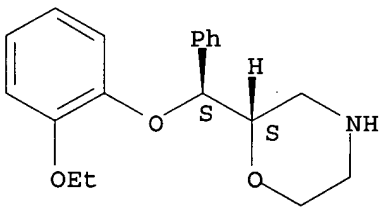

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CN FCE 20124
CN PNU 155905E
CN PNU 155950E
CN Reboxetine mesylate
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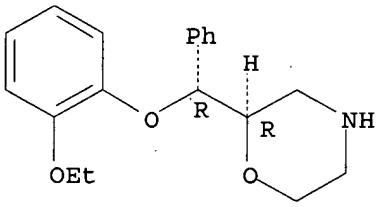

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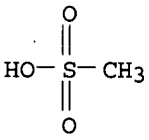

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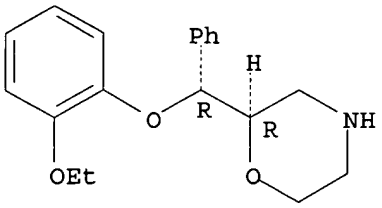

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DOCUMENT NUMBER:          144:292415
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                          nervous system disorders
INVENTOR(S):              Claffey, Michelle, Merie; Fliri, Anton, Franz, Josef;
                          Gallaschun, Randall, James; O'Donnell, Christopher,
                          John
PATENT ASSIGNEE(S):       Pfizer Products Inc., USA
SOURCE:                   PCT Int. Appl., 86 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
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Peripheral Neuropathy and HIV

Michael J. Polydefkis, M.D.

The Hopkins HIV Report - July 2002

Peripheral nerve damage is one of the most common neurological complications of HIV infection and its **treatment**. Of these, the distal sensory neuropathies, which occur in the advanced stages of HIV disease, are the most common, affecting approximately 30% of AIDS patients. It is important, however, to recognize that other forms of **peripheral** nerve disease occur in HIV infection. Many are caused by other infectious agents and are therefore potentially treatable. This **article** will briefly **review** less common forms of **peripheral** nerve injury in HIV and will then focus on the HIV associated sensory neuropathies.

[Return to top]

Peripheral Neuropathies other than HIV Associated Sensory Neuropathies

In the early phase of HIV disease, patients may develop acute or chronic inflammatory demyelinating **neuropathy** (AIDP, CIDP). AIDP, also known as Guillain Barré syndrome (GBS), can be the initial manifestation of HIV infection and is indistinguishable clinically and electrophysiologically from that seen in uninfected patients. One feature of HIV-associated AIDP is a mononuclear CSF pleocytosis accompanying elevated CSP. This contrasts with non-HIV GBS in which there are typically no cells in spinal fluid. The precise epidemiologic figures of AIDP in HIV disease are unknown, though there is some evidence that the pleocytosis from HIV infection is directly related to the **neuropathy**. The mainstay of **treatment** is plasmapheresis and IV immune globulin, and the prognosis does not appear to be different from non-HIV associated AIDP.

CIDP (Chronic inflammatory demyelinating polyneuropathy) may also be the presenting illness for HIV disease and generally occurs with CD4 counts between 200-500 cells/mm^3. This condition can be thought of as a chronic form of GBS. Patients typically have absent or reduced reflexes as well as patchy numbness and weakness. CSF examination often shows a mild, mononuclear pleocytosis in addition to an elevated protein. **Treatment** centers on immunomodulation and is potentially problematic in the setting of HIV disease given the pre-existing immuno-suppression. Corticosteroids, plasmapheresis, IVIG and cyclosporin have all been used successfully. No clear guidelines for anti-retroviral therapy exist, though it seems prudent to avoid potentially neurotoxic agents.

Mononeuropathies such as Bell's palsy have been suggested to occur at higher rates in HIV-infected people, though precise figures are unknown. Mononeuropathy multiplex (MM) can occur early in HIV disease as a result of immune dysfunction or vasculitis. Clinically, these patients have asymmetric, patchy sensory or motor deficits. In vasculitis, pain generally precedes motor or sensory deficits. Nerve biopsy is necessary to confirm the diagnosis. Electrodiagnostic testing is helpful in confirming asymmetric abnormalities, excluding multiple entrapment neuropathies as well as in identifying an appropriate site for biopsy. Therapy is determined by etiology, with vasculitis requiring immunosuppression.

An often painful, distal sensorimotor **neuropathy** associated with CD8 hyper-lymphocytosis and a Sjögren's-like syndrome can occur during symptomatic HIV infection and potentially could be confused with
HIV-associated sensory **neuropathy**. This disorder has been termed diffuse infiltrative lymphocytosis syndrome (DILS). Only patients with CD8 hyperlymphocytosis and MHC class HLA DR5 or DR6 alleles appear to be at risk, and the mean CD4 cell count in DILS patients is 260 cells/mm^3, with one third having AIDS. Clinically, DILS develops as a subacute, often painful **neuropathy** commonly accompanied by parotid enlargement and sicca syndrome. Many patients have systemic involvement, such as lymphadenopathy, splenomegaly or intersitial pneumonia. Electrodiagnostic testing generally reveals a length-dependent axonal process, though evidence of demyelination is present in 15% of cases. CSF analysis is notable for a nonspecific mononuclear pleocytosis and striking xanthochromia. Pathology reveals a non-destructive angiocentric T cell infiltrate in the epi- and endoneurium. **Treatment** is centered on HIV suppression, with HAART resulting in complete recovery in two-thirds of patients.

A progressive polyradiculopathy (PP) can develop in patients with advanced HIV disease and CD4 cell counts of 50 cells/mm^3 or less. Patients usually present with subacute low back and radicular pain over a period of days. Weakness progresses to flaccid paralysis with sensory loss and frequently urinary difficulties. The upper extremities are rarely involved. The most common cause is CMV, with approximately 10% of cases occurring while on CMV maintenance therapy and 38% having evidence of CMV infection elsewhere, usually retinitis. Other causes include lymphomatous meningitis, syphilitic radiculopathy, herpes simplex or herpes zoster myeloradiculopathy, toxoplasmosis, and mycobacterial infection. CSF analysis is essential in distinguishing among these possibilities. A predominant polymorpho-nuclear pleocytosis, commonly above 200 cells/mm^3, with a low CSF glucose is typical of CMV infection. CSF cytology, VDRL and viral PCR studies are also useful, while imaging studies are important in ruling out mass lesions. Early recognition and **treatment** of CMV polyradiculopathy can prevent an otherwise devastating outcome.

A mononeuropathy multiplex occurring in the setting of advanced HIV disease is almost always due to CMV infection. As with CMV polyradiculopathy, evidence of CMV infection elsewhere is common, particularly in the retina. CSF analysis in CMV mono-**neuropathy** multiplex **differs** from CMV PP in that a polymorphonuclear pleocytosis is often not present, though CMV PCR is usually positive. Most patients improve after **treatment** with foscarnet or ganciclovir.

[Return to top]

The HIV Associated Sensory Neuropathies

The most common **peripheral** nerve complication in HIV infection is a length-dependent, axonal sensory **neuropathy** that is dominated by neuropathic pain. The HIV associated sensory

neuropathies (HIV-SN) include both distal sensory polyneuropathy (DSP) due to IV infection, and antiretroviral drug toxic **neuropathy** (ATN) caused by the dideoxynucleosides (ddC, d4T, and ddI). These two forms of HIV-SN are pheno-typically identical and affect approximately 30% of AIDS patients. They are characterized by painful dysesthesias in the feet and legs, described as "painful numbness," "aching," or "burning." HIV-SN is a major source of morbidity among AIDS patients. Symptoms are generally worse at night and can be aggravated by innocuous stimuli, such as bed sheets or wearing shoes. Abnormalities on examination are generally limited to sensory nerve fibers and include reduced or absent ankle reflexes and increased vibratory and pin thresholds. Affected patients can often test normally on routine nerve conduction testing. This reflects the prominent small caliber sensory nerve involvement in HIV-SN and the fact that these nerves are "invisible" to nerve conduction/EMG testing. Skin biopsy and visualization of epidermal nerve fibers is a useful diagnostic tool in such instances.

DSP is associated with advanced HIV disease, with lower CD4 count and higher viral load being risk factors. An association between viral set point and the subsequent development of HIV-SN has been suggested. Autopsy studies have demonstrated pathological abnormalities in the **peripheral** nerves of virtually all patients dying from AIDS, and sub-clinical abnormalities in **peripheral** nerve function are common on detailed testing. This suggests a gradual progression of nerve damage in HIV disease with much of it being silent, before development of DSP. HIV itself appears to play an indirect role in the development of DSP in that macrophage activation and aberrant proinflammatory cytokines are thought to mediate the neurotoxicity.

While the incidence of most neurological complications of HIV has fallen dramatically over the past decade, HIV-SN has become more prevalent, coinciding with the use of dideoxynucleoside drugs. ATN has sub-sequently emerged as a common cause of HIV-SN.

The only distinguishing characteristic of ATN is the temporal association with use of dideoxynucleoside NRTIs; otherwise the two conditions are virtually indistinguishable. The onset of ATN ranges from one week to 6 months, depending on the NRTI and the dose administered. Symptoms may continue to worsen after discontinuation of the offending agent, followed by improvement in most but not all patients over a period of weeks to months. Pathophysiologically, ATN **differs** from DSP and has been linked to mitochondrial dysfunction. Importantly, patients with pre-existing DSP appear to be at increased risk of developing ATN. Dideoxynucleoside NRTIs may trigger neuropathic symptoms in patients with pre-exiting, silent neuronal damage due to HIV infection.

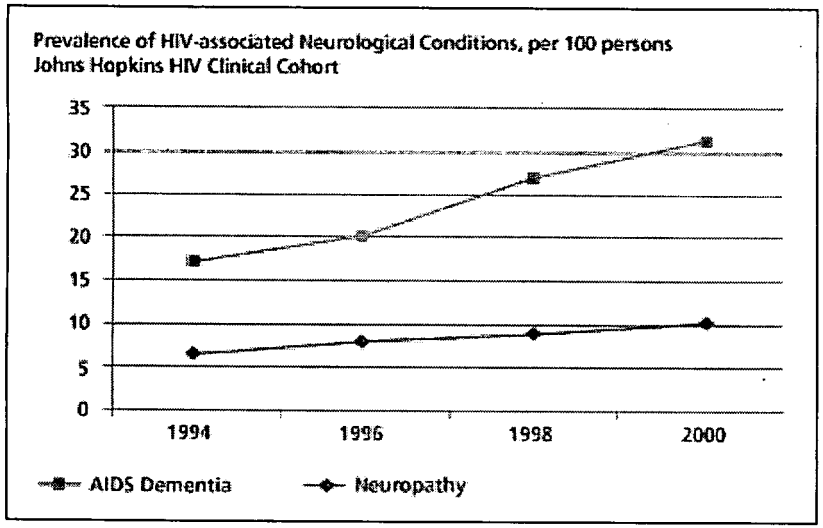
Treatment of HIV-SN is largely symptomatic. In the case of ATN, the suspected offending agent should be discontinued or the dose reduced, if possible. Several agents that have been effective in other painful neuropathies have not shown efficacy in HIV-SN, including amitriptyline, mexiletine, topical capsaicin and acupuncture. Both 5% lidocaine and gabapentin have been used successfully in open-label trials, but controlled data is lacking. Anecdotal evidence suggests that topiramate may also be beneficial. Currently, the only therapies shown to be effective in randomized, placebo-controlled clinical trials are lamotrigine and recombinant human nerve growth factor, of which the latter is not commercially available. The beneficial effect of lamotrigine appears to be most pronounced in ATN patients, and the risk of rash is minimal if the dose is slowly titrated upwards. Both lamotrigine and topiramate have the added advantage of not affecting the cytochrome P450 pathway and therefore not interacting with antiretroviral agents.

[Return to top]

Conclusions

Peripheral nerve disease is common in HIV infection. Other infectious causes are infrequent but important to recognize, as they are potentially treatable. HIV-SN is the most prevalent **neuropathy** associated with HIV infection and is now the most common neurological complication of HIV disease. Two forms of HIV-SN exist, distal sensory polyneuropathy (DSP) related to macro-phage and cytokine dysregulation resulting from HIV infection and antiretroviral toxic **neuropathy** (ATN), produced by mitochondrial dysfunction. ATN can require alteration of antiviral regimens at the risk of reducing virologic control and may act to trigger or unmask clinically silent HIV-mediated **neuropathy**.

Dr. Polydefkis is an Assistant Professor of Medicine in the Department of Neurology, Johns Hopkins University, School of Medicine.



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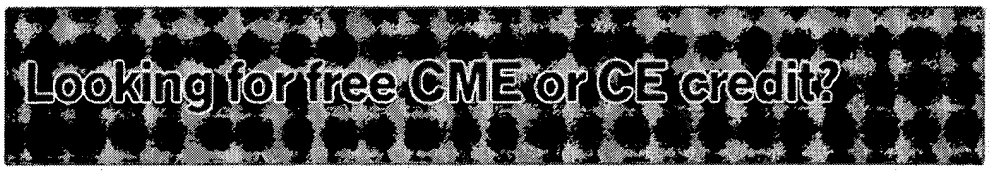

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Peripheral Neuropathy

May 1998

Table of Contents

- References

Peripheral neuropathy (PN), or damage to the **peripheral** nerves (nerves outside the brain or spinal chord), is a potential side effect of many anti-HIV therapies or HIV itself and can greatly affect quality of life. It is often caused by a breakdown of the myelin sheath, the coating around nerve fibers that acts as an electrical insulator. Early signs of PN can include a sensation of burning, tingling, or numbness in the fingers or toes. Some people describe an electric shock sensation or a strange plastic or scab-like sensation when something touches their fingers or toes. In severe cases, touching the affected area can feel like touching an open wound. In some cases, there may be a deep soreness or shooting pains in the muscles of the legs and lower arms that may be transient but always affect the same general area. In more serious cases, severe pain and altered feedback in the nervous system may even interfere with walking.

Currently, there are no effective treatments that can stop or reverse this nerve damage. The most effective management of PN includes identifying the cause and, if possible, eliminating it. In many cases, the best treatment is simply pain management, and the type of medication used is generally determined by the severity of the PN.

Neuropathy can also be caused by HIV itself, and it's hard to know whether the disease or its treatment is causing the problem.

Neuropathy can be caused by certain drugs, most commonly ddC (Hivid), ddI (Videx), 3TC (Epivir), d4T (Zerit), isoniazid (INH), vincristine (Oncovin), dapsone and vitamin B_6. Combination therapy with two or more of these drugs is believed to increase the risk of PN, though this is not well documented. PN will often go away if these drugs are changed, dose-reduced, or discontinued. It can sometimes take several months for PN to fully heal after removing the problematic drug, though some relief is often felt within a few weeks. In the most severe cases, **peripheral neuropathy** may never heal. It is critical to consult a physician before changing a drug regimen, as dose reduction of certain drugs can invite drug resistance. Be aware also that sometimes the symptoms of PN increase temporarily after a drug is stopped, but diminish soon thereafter. In some cases, if drugs are continued despite worsening PN, the nerve damage may become irreversible.

People with a history of diabetes or thyroid disease may have a greater likelihood of PN. Alcohol use or deficiency of vitamins B_{12} and E can also cause PN. In such cases, a physician can help design a treatment strategy for the condition. For vitamin B_{12} deficiency, vitamin B supplements may help, but too much vitamin B_6 (over 200mg per day) can worsen PN.

If the cause of PN can't be clearly identified (i.e., it may be due to HIV itself), or if the problem does not correct itself after stopping the drugs that may have caused it, chronic pain management may be required. Choice of treatment depends on the severity of symptoms. In the case of HIV-induced PN, some of the same drugs that potentially cause the problem may, in some cases, help relieve it.

For mild symptoms (tingling sensations but no problems walking, etc.), some people use a conservative strategy of simply observing the symptoms. Others find that mild pain can be relieved by using non-narcotic pain relievers such as ibuprofen (Advil) at doses of 600-800mg 2-3 times daily.

For moderate symptoms (pain and can't walk as far as desired), people can take antidepressants such as amitriptyline or nortriptyline (mood elevators), combined with mild pain relievers. However, mood elevators are not approved for treating PN, and are believed to work best only when combined with traditional pain medications. Mexilitine, a drug used to treat irregular heart rhythms, is also sometimes used to treat PN, although in clinical trials it has shown little effect.

Severe symptoms include constant pain and the inability to walk or sleep at night. When experiencing this level of pain, it is recommended that you see a pain specialist. Specialists will have far more experience treating severe, chronic pain than most HIV physicians. They are also more experienced in managing high level narcotics and the associated problems. In severe cases, physicians may prescribe narcotic pain relievers such as methadone, a fentanyl patch, vicodin, morphine or codeine (see section on "Pain Relievers" for more information). Of these, methadone is least likely to be accompanied by the typical dulled sensations and euphoria associated with narcotics.

When the pain from PN is so great as to be seemingly untreatable (rarely), a pain specialist may recommend a "nerve block." In this procedure, a fluid, typically alcohol, is injected directly into a major nerve junction just above the sight of the worst pain. When they work, nerve blocks can be very effective and cause long-term reduction or elimination of pain. However, a major consideration is that they usually cause loss of sensation, and in worst-case scenarios, can be unpredictable. Clearly, nerve blocks should only be attempted by a specialist, and even then only after getting a second or third opinion.

Managing Neuropathy

None of the following suggestions have been formally studied, yet care providers and others offer them as suggestions for helping manage the symptoms of PN. For severe and prolonged pain, seeing a pain management specialist is key to developing a workable strategy.

- **Avoid tight-fitting shoes and socks.** People sometimes think that tight shoes can help with numbness and prevent rubbing, but they can actually exacerbate the pain and tingling. Many people find soft, loose cotton socks or loose, padded slippers to be helpful. Shoes should be neither tight nor excessively loose, and should offer good air circulation if possible.

- **Be sensitive to temperature.** Most people report that **neuropathy** feels worse in hot weather or when feet are heavily covered and don't have much opportunity for air circulation.

- **Keep feet uncovered in bed.** Bed sheets resting on your toes can also add to the problem. Some people use a semicircular hoop on which they rest their sheets to avoid contact. The important thing is to keep your feet uncovered at night. This helps keep the temperature down (which may help serious pain to "numb out") and also prevents friction between the sheets and toes.

- **Get up and walk around!** Although it may seem contradictory for people who are in pain and can't walk, getting blood to the feet by walking

around can help relieve some of the pain. Too much walking, however, will only make the problem worse. A moderate amount of activity can distract a person from fixating on the pain, without adding to it.

- **Some people try acupuncture.** While this can often bring quick relief, many people report that the relief does not last for long and requires very frequent treatment.

- **Deep tissue massage.** Simply massaging sore feet helps improve circulation. Perhaps more importantly, it causes all the available neurons in that part of the nervous system to "fire." Once they "fire" or give off the chemical signal by which pain is transmitted, they must rest awhile before they can do so again. The result is that the pain is temporarily dulled. This is the same phenomenon as massaging any sore spot on the body.

- **Soaking feet in cool water.** When pain is severe, perhaps too strong to allow a person to sleep, water treatment can help. Put sore feet in a large dishpan (or special devices made for this purpose) and gradually fill with room-temperature water. Once filled, let the water keep running gently while you lower the temperature. The water will slowly become colder and eventually reach a point where most pain has stopped. Dry your feet off and go to bed, hopefully getting to sleep before the pain returns. This is also a good tactic to use while waiting for a pain medication to "kick-in."

- **Biofeedback.** Many people can be "trained" to deal with mild-to-moderate pain, largely by learning to divert their minds away from it. The pain from PN, after all, is not signaling any real harm to the body, as pain usually does. Some people ignore the pain and sensations of PN or live with them simply by learning to perceive them differently.

There are a few experimental therapies in clinical trials for the treatment of **peripheral neuropathy**. Nerve Growth Factor (NGF) may help repair damaged nerves. Early reports suggest that it may be useful in eliminating the most severe, shooting pains associated with **neuropathy**, but results will not be released until mid-1998. Lamictal (lamotrigine) and gabapentin are both approved antiseizure drugs that may be of use in treating **neuropathy**.

Nerve Growth Factor

New Treatment Shows Promise for Peripheral Neuropathy

Excerpted from an article by Matt Chappel, ACT UP/Golden Gate

Recombinant human Nerve Growth Factor (rhNGF) may be the first treatment that actually repairs nerves damaged by HIV or drugs used to treat HIV infection. rhNGF is a manufactured form of a naturally produced chemical that signals the body to produce, repair and strengthen small nerves. These are the types of nerves damaged in HIV associated **Peripheral Neuropathy** (PN). No other therapy used in the management of PN symptoms repairs the damage, but they may alleviate some of the pain and help to cope with the situation.

rhNGF is currently being studied in ACTG (AIDS Clinical Trials Group) study #291, a phase II study conducted by the government's main AIDS trial network. ACTG #291 compares two doses of rhNGF to placebo and is designed to evaluate the effectiveness of rhNGF in the treatment of **peripheral neuropathy** caused by HIV or antiviral treatments. Subjects may take any medications to control pain.

Genentech claims that a major production problem occurred when attempting to create enough drug for a 1600 person diabetic **neuropathy** study, and that consequently supplies of the drug are very limited even for trials such as ACTG 291. According the to company, these supply problems have been resolved and drug will be supplied to those continuing on ACTG 291 at the end of February 1997. This is largely due to continued pressure from advocacy groups such as ACT UP/Golden Gate and Project Inform.

Genentech recently presented results of a phase II diabetic **neuropathy** study at the American Neurological Association Meeting in Miami, Florida. Results of the 250 person study indicated that there was an overall reduction in pain measured by "accepted pain scales" for those who received rhNGF but not the placebo group. In addition to this, there was an increase in sensation to hot and cold in subjects receiving rhNGF. There seemed to be no dose-related difference between the two doses of rhNGF studied, so they will continue development of the lower dose. The only side effect when given correctly is soreness at the site of injection. Genentech also reported that those who received rhNGF had a return of **neuropathy** after they went off of rhNGF.

Peripheral neuropathy (PN) is one of several types of nerve damage that can occur in AIDS. It is painful and debilitating and 30% of people with AIDS will develop symptoms of **peripheral neuropathy**. The most common forms of PN in AIDS are Distal Symmetrical Polyneuropathy (DSPN) caused indirectly by HIV, and neurotoxic **neuropathy** caused by the side effects associated with many of the drugs used to treat HIV disease. D4T, ddI, ddC, 3TC, Isoniazid (a tuberculosis drug), Vinblastine (a cancer drug commonly used to treat Kaposi's Sarcoma), Cisplatin (a cancer drug) and Taxol (a cancer drug) are some that may cause toxic neuropathies. Seven to fifteen percent of PWA's on the antiretroviral treatments named will develop PN from those treatments. If PN is caused by a drug, the symptoms will sometimes go away 6-8 weeks after the drug is stopped (sometimes the **neuropathy** continues to worsen, prior to resolving, after drug is discontinued). Even some drug-induced neuropathies, however, become long-lasting or permanent. Usually someone cannot attempt to use the drug again with out having the PN return. Sometimes a toxic **neuropathy** can enhance a pre-existing form of PN that does not stop when the drug is stopped.

Symptoms of DSPN and neurotoxic neuropathies are similar. DSPN Is characterized by a burning pain that will start in the middle of the toes and fingers, a numbness and/or tingling as if you are wearing stockings and gloves, pain that occurs during normal use of hands and feet such as walking and the loss of ability to flex tendons in the ankles and wrists. Symptoms persist for a long time following onset and occur at a greater rate in advanced AIDS. Other diseases can cause neuropathies too. Alcoholism, diabetes, vitamin B-12 deficiency, some inflammatory diseases, hypothyroidism and neurosyphilis may also cause DSPN. If you are experiencing any of these or other neurological symptoms, it is highly suggested that you see a neurologist experienced with AIDS.

How HIV can damage nerves is poorly understood and has been inadequately studied. HIV is known to infect a type of blood cell called macrophages whose job is to fight disease. Macrophages can infiltrate the myelin that acts as an insulator

for signals traveling through the nerves, much like the rubber coating insulates the electrical signal in a wire. When this occurs, the macrophages may begin to damage the myelin. Macrophages may also cause the increase in chemicals used to signal the immune system that an inflammation exists and needs attention. Tumor Necrosis Factor is one of these chemicals found to be increased in DSPN from AIDS and believed to have a role in DSPN.

DSPN is currently treated with a variety of strategies that may include occupational therapy, physical therapy, and most commonly, tricyclic **antidepressant** medications. The most common is Amitriptyline (elavil). Others include disiprimine and imiprimine. These drugs do not necessarily alleviate the pain, they increase sleepiness and cause severe dry mouth, but you may not care so much about the situation. Mexilitine (a cardioarrythmia drug) is also frequently prescribed and may be used in combination with tricyclic and pain medications.

Pain relieving drugs used are usually opiate-based and include; morphine, codeine, oxycodone, vicodin, methadone and fentanyl patches. If tricyclic drugs fail, anticonvulsant medications such as phenytoin, carbemazepine and recently gabapentin (neurontin) may be given a chance. Acupuncture and vitamins B-6 and B-12 are other means of attempting to treat PN, but like drugs, these require continuous use. Sometimes, as you can see, finding the right combination can be a long process. It may involve management of side effects. For example, large doses of opiate-based drugs can produce a sense of euphoria, are definitely habit forming, cause constipation and may inhibit someone from functioning at their normal level.

Vitamin combinations have been used for years in diabetic **neuropathy**, the most common **neuropathy**. There have been no controlled studies with these compounds in AIDS but some people report improvement and additional relief of symptoms. Caution is urged with vitamin B-6 (thiotic acid) since it will cause PN if used at doses greater than 500mg per day. B-6 is usually prescribed at 50mg per day doses and has been shown to effectively treat **neuropathy** caused by the anti-TB drug, Isoniazid (INH). The same dose is used for diabetic **neuropathy**.

Current studies (other than ACTG 291) include another ACTG study #242 and one CPCRA study. ACTG 242 is designed to establish a standard treatment and to truly evaluate the effectiveness of Amitriptyline compared to Mexilitine in the treatment of DSPN. Both are widely used, but neither has yet really been proven to be effective. The study is slow to accrue since the drugs are already available. The CPCRA is conducting a study of acupuncture with Mexilitine compared to "sham acupuncture" (using false acupuncture point locations) as a placebo. Recently, CPCRA conducted a small study of Mexilitine compared to placebo that seemed to indicate that at least subjectively, there was improvement in pain among those receiving the drug. Placebo arms are commonly used in pain-related studies since there is a definite placebo effect that can confuse study results. For example, Peptide T (a type of protein), was studied for treatment of DSPN and results indicated that subjects on the placebo (saline) reported greater improvement than those on the treatment arm.

Memantine is another potential drug for DSPN. Memantine is approved in Germany for Parkinson's disease where it has been used for the last 15 years. Memantine is currently in two studies; ACTG #301 for treatment of AIDS-related dementia, and the other at the National Cancer Institute for diabetic **neuropathy**. There is no current study of the drug for HIV associated **neuropathy**. The drug is available through the PWA Health Group in New York.

Treatments for DSPN have been only marginally successful in improving the quality of life for those with AIDS. rhNGF is the only compound that may protect, or even repair damaged nerves making it an important potential treatment that may enable people to continue antiretroviral treatment.

Diagnosis and Management of Sensory Neuropathy in HIV Infection

Reprinted from AIDS Clinical Care, 2/94, pages 9-12,16 by Gerald J. Dal Pan, MD and Justin C. McArthur, MD, BS

Peripheral neuropathy may be the most frequent neurologic disorder associated with HIV infection; its symptoms cause substantial morbidity and discomfort to patients with AIDS. This article will concentrate on the two most common HIV-associated neuropathies: predominantly sensory **neuropathy** and medication-induced toxic **neuropathy**.

Epidemiology

The prevalence of sensory **neuropathy** is relatively low during asymptomatic HIV infection. However, a 30% to 35% prevalence of **peripheral neuropathy** has been documented in both referral-based cohorts of medically symptomatic HIV-infected individuals and hospital-based studies of consecutive AIDS admissions.[1,2] The annual incidence in AIDS patients with CD4 counts of less than 100 cells per ml is 8%.[3]

Clinical Features

The most common **peripheral neuropathy** associated with HIV occurs in the later stages of HIV disease, usually after the patient has had other AIDS-defining illnesses. This disorder, called predominantly sensory **neuropathy** (PSN) or distal symmetric polyneuropathy (DSPN), occurs in over 30% of individuals with AIDS. Autopsy-based studies have found it in nearly 100% of patients who died of AIDS. Because the symptoms of PSN are virtually identical to those of the toxic neuropathies (TN) associated with the antiretroviral agents ddI, ddC and d4T, the two classes of **neuropathy** will be considered together in this article.

The diagnosis of a sensory **neuropathy** requires a history compatible with predominantly sensory dysfunction and a physical examination notable for abnormal sensory findings in the feet, with reduced or absent ankle jerks. Ancillary testing is required in only a minority of cases.

History

As the name implies, sensory disturbances are by far the predominant symptoms of PSN. Early in the course of the disorder, dysesthesias confined to the soles may occur. After a few to several weeks, the se dysesthesias tend to ascend symmetrically and, by the time the patient seeks medical attention, have usually reached the ankle. Sensory complaints can be elicited from patients, varying from on individual to the next. Patients describe these sensations as burning, tingling, shooting pain, numbness, throbbing, aching, and "feels like frostbite" or "walking on a bed of coals." An accurate record of the patients neuropathic symptoms is

important, since treatment may alleviate some, but not all, symptoms.

In some patients the skin develops hyperalgesia, exquisite tenderness to touch exacerbated by bedsheets, sock and tight-fitting shoes; in some instances, pain limits walking. Patients with lower extremity complaints limited to the feet and ankles may note similar symptoms in the fingertips; as the process extends to the knees, it may also extend to the wrists. Only rarely will patients complain of these symptoms above the knees. Patients may complain of mild muscle weakness, but this is not a distinct feature. Bowel and/or bladder disturbances are not seen in HIV-associated sensory neuropathies; their presence should prompt a search for other etiologies.

A second element of history-taking is excluding other causes of sensory **neuropathy**. A variety of neurotoxic medications-commonly the antiretroviral agents ddI, ddC and d4T-can result in a dose-dependent similar to those of PSN (Tables 1 and 2).

Table 1: Potentially Neurotoxic Substances Commonly Used by HIV-Positive Individuals

Didanosine (ddI)
Zalcitabine (ddC)
Stavudine (d4T)
Metronidazole
Isoniazid
Pyridoxine (vitamin B_6)
Vincristine
Dapsone
Alcohol

Whether this represents direct neurotoxicity or unmasking of a silent or latent PSN remains unclear. Frequently, individuals who have mild neuropathic symptoms prior to the initiation of ddI, ddC or d4T experience an intensification of symptoms when started on one of these agents. (Toxic **neuropathy** has not been noted in association with AZT.) Symptoms can begin any time after the agent has been started, but typically occur after several weeks on the drug. Symptoms may also worsen for up to 4 weeks after discontinuation of the agent, a phenomenon known as "coasting." Many patients whose symptoms resolve after stopping the drug are able to resume it at half the previous dose.

All patients should be asked about a history of diabetes or excessive alcohol consumption, as there are other common causes of **peripheral** neuropathies and may predispose patients with HIV to PSN or TN.

Where sensory symptoms spare the top of the foot and are limited to the anterior portion of the sole, the clinician should suspect tarsal tunnel syndrome-entrapment of the plantar nerves as they pass through the tarsal tunnel in the ankle, just below the medial malleolus. If light tapping in the rea just beneath the medial malleolus causes shooting pains into the sole (positive Tinel's sign), the patient probably has tarsal tunnel syndrome.

Table 2: Differential Diagnosis of Lower Extremity Symptoms in HIV Infection

Syndrome	Symptoms	Clinical Features	Ancillary Studies/Treatment
Predominantly Sensory Neuropathy	Pain and numbness in toes and feet; ankles, calves and fingers involved in more advanced cases	Reduced pinprick/ vibratory sensation. Reduced or absent ankle jerks. Contact hypersensitivity present in some cases	Electromyography/nerve conduction velocities (EMG/NCV) show a predominately axonal **neuropathy**. See flow sheet for treatment
Toxic Neuropathy	Same as PSN (above) but symptoms occur after initiation of ddI, ddC, d4T	Same as PSN (above)	EMG/NCVs show a predominantly axonal **neuropathy**. Discontinuation of presumed neurotoxic medication. Symptoms may worsen for a few weeks ("coasting") before improving. See flow sheet for treatment.
Tarsal Tunnel Syndrome	Pain and numbness predominantly in anterior portion of soles of feet	Reduced sensation over soles of feet. Positive Tinel's sign at tarsal tunnel	Infiltration of local anesthetic into tarsal tunnel may provide symptomatic relief.
HIV-Associated Myopathy/ AZT Myopathy	Pain and aching in muscles, usually in thighs and shoulders. Weakness, with difficulty arising from a chair or reaching above shoulders	Mild/moderate muscle tenderness. Weakness predominantly in proximal muscles (i.e. deltoids, hip flexors). Normal sensory exam/normal reflexes	Creatine phosphokinase (CPK) usually elevated. EMG/NCVs show evidence of an irritable myopathy. If patient is on AZT, discontinue AZT and follow every 2 weeks. Symptoms/signs/ CPK should improve within 1 month.
Polyradiculitis	Rapidly evolving weakness and numbness in legs (both proximally and distally), with bowel/bladder incontinence	Diffuse weakness in legs. Diffuse sensory abnormalities in legs and buttocks. Reduced/absent reflexes at knees and ankles.	EMG/NCV shows multilevel nerve root involvement. Spinal fluid helpful in determining etiology (cytomegalovirus or herpes simplex virus infections, lymphomatous infiltration). Ganciclovir helpful in CMV polyradiculopathy.
Vascular Myelopathy	Stiffness and weakness in legs with leg numbness. Bowel/bladder incontinence in advanced cases	Weakness and spasticity mainly in hip flexors, knee flexors, ankle dorsiflexors. Brisk knee jerks, upgoing toes (Babinski's sign). If sensory **neuropathy** co-exists, then distal sensory loss and	Spinal fluid may show elevated protein, mild (5-10 cells/mm^3) or no pleocytosis. Thoracic spinal imaging normal. No specific therapy. Physical therapy often helpful

		reduced/absent ankle jerks will also be seen	
Inflammatory Demyelinating Polyneuropathies	Predominantly weakness in arms and legs, with minor sensory symptoms	Diffuse weakness including facial musculature, asymmetric in early cases, with diffuse absent reflexes. Minor sensory signs	EMG/NCVs show a demyelinating polyneuropathy. Spinal fluid show very high protein, with mild to moderate lymphocytic pleocytosis, but all cultures are negative.

Physical Findings

The physical examination is similar whether it is PSN or TN that is suspected (Table 2). An exam directed to diagnosis of these conditions can be performed in 1-2 minutes.

Contact Hypersensitivity
Contact hypersensitivity may be elicited by lightly stroking the plantar and dorsal surfaces of the feet.

Motor Testing
Proximal leg musculature (hop flexors, knee flexors and knee extensors) should be normal. About a third of patients with sensory **neuropathy** exhibit mild intrinsic foot muscle weakness (i.e., weakness of extending, curling, spreading of toes).

Pain
Pain and vibratory sensation are abnormal in most patients with these neuropathies. Pain sensation is assessed by lightly applying the pint of a pin to the skin and asking the patient if it feels sharp. To familiarize the patient with this stimulus, it is sometimes helpful to first test pinprick sensation in an unaffected area such as the distal forearm. Then the pin is applied to the toes and "marched up" the dorsum of the foot to the ankle, and along the calf to the knee. The patient is asked if the pin feels equally sharp throughout. Most patients with sensory **neuropathy** have some abnormality of pin sensation in the toes and over the dorsum of the foot. They will note that the pin is not quite as sharp there as in other areas, that is "just doesn't feel the same." Some patients have said "it feels as if my socks were still on." Others note that the pin feels more painful in affected areas than in the parts of the body not affected by **neuropathy**. Only in more advanced cases will abnormal sensation extend above the ankles; in those cases, some abnormalities in the fingertips may also be noted.

Vibratory Sensation
Vibratory sensation is best assessed by applying a 128 Hz tuning fork over the great toe. Patients with sensory **neuropathy** will generally fell the "buzzing" for only a few seconds; most patients who perceive a "buzz" for more than 10 seconds have normal vibratory sensation.

Ankle Jerk
The vast majority of patients with **neuropathy** have either absent or reduced ankle jerks. If ankle jerks are difficult to elicit with the patient seated, it is often helpful to have him or her kneel on a chair, facing the back of the chair with the feet dangling off the seat. With the patient in this position, a tap on the Achilles

tendon often elicits the ankle reflex. It may be necessary to ask the patient for a reinforcement maneuver-such as clenching the fists or jaw-to bring out a "trace" reflex. If no reflex is elicited even with reinforcement, the ankle jerk reflex is considered.

Tinel's Sign
Finally, as described above, the physical exam in all patients with a suspected sensory **neuropathy** should include tapping the area just beneath the medial malleolus, which will elicit a positive Tinel's sign in patients with tarsal tunnel syndrome. Tinel's sign will not be elicited in patients with PSN or TN.

Ancillary Studies

Nerve-conduction-velocity studies with electromyography reveal oss of axons in both sensory and motor nerves. These studies are generally of little value in the management of patients with the typical features of PSN or TN but may be helpful in patients with other neuromuscular manifestations of HIV infection. Nerve biopsy is only rarely indicated in PSN, and is usually reserved for those in whom diagnosis is uncertain, for example, where vasculitis is a concern.

Differential Diagnosis of Suspected Neuropathy

The evaluation should exclude other neurological syndromes which can produce sensory and/or motor disturbances in the legs. These entities are summarized in Table 2 (above).

Evaluation of Sensory Neuropathy

- Once the diagnosis of a sensory **neuropathy** has been established, its cause should be ascertained.

- Vitamin B_{12} levels, thyroid function tests, and a glucose level should be obtained to screen for potentially reversible neuropathies.

- In individuals with AIDS but without a history suggesting a nutritional or neurotoxic **neuropathy**, HIV-associated PSN is the most common diagnosis.

- In individuals with AIDS who are currently taking ddC or ddI and whose symptoms developed at least several weeks after the initiation of the agent, a toxic **neuropathy** must be the presumptive diagnosis. If the symptoms persist for several months after the antiretroviral has been stopped, a coexistent HIV-associated PSN is likely to be present. This logic applies to other potentially neurotoxic medications as well (see Table 1 above).

- In patients with both diabetes and AIDS, it is virtually impossible to separate the components of the **neuropathy** due to diabetes and to HIV-associated PSN, although prominent motor signs are more likely the result of diabetes.

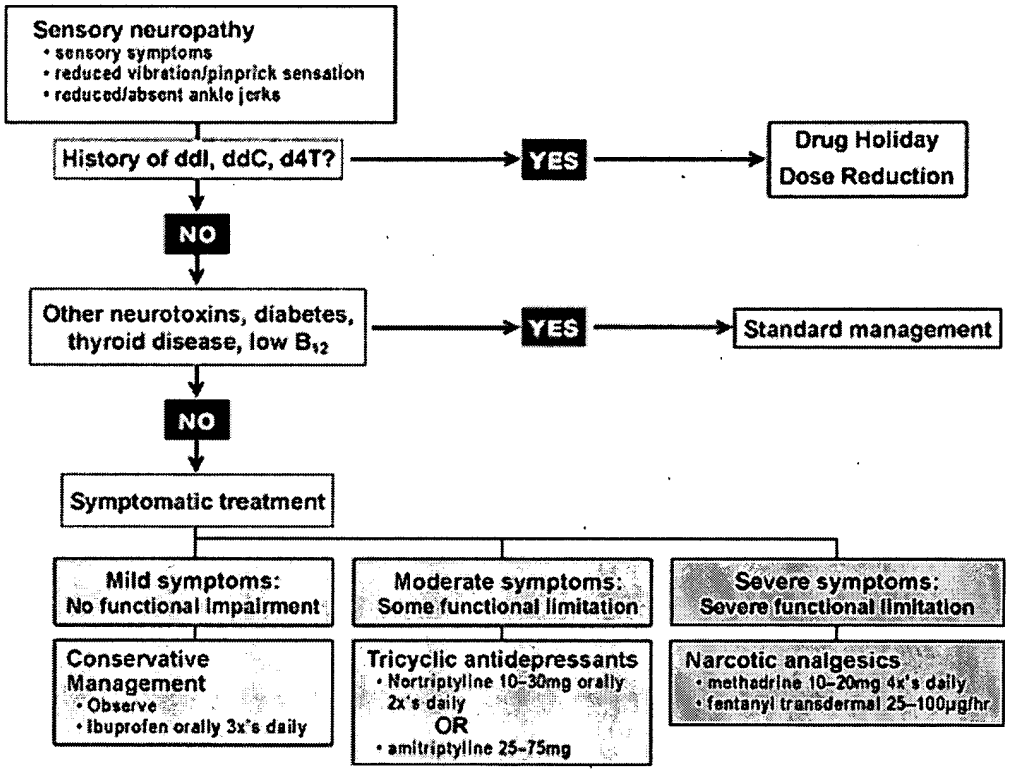
- In HIV-infected diabetics without advanced immunodeficiency (CD4+ cell

count > 300), **peripheral neuropathy** should be attributed to the diabetes rather than to HIV-associated PSN.

Management of Sensory Neuropathy

Management of sensory **neuropathy** is targeted to relief of painful neuropathic symptoms (see Fig. 1). Research is in progress on agents (including nerve growth factor) to reverse nerve fiber destruction, and clinical trials are being planned. However, no therapies exist currently that halt or reverse nerve fiber destruction.

Figure 1. Algorithm for Management of Sensory Neuropathy



Nonpharmacologic Management

Many patients develop physical practices which help them relieve pressure on hypersensitive feet. These include avoiding tight footwear, walking only short distances, avoiding standing for long periods, and periodically soaking the feet in ice water. For some patients, these maneuvers are sufficient, and they do not require medications.

Pharmacologic Treatment

Symptomatic treatment with pharmacologic agents is largely empiric; no large-scale controlled trials have been conducted in the HIV population. Unfortunately, no specific characteristics of the pain can predict which agents will be beneficial. Choice of medication is based on the severity of the patient's symptoms and the side-effect profile of the medication. Patients with mild pain that is not functionally limiting may tolerate their symptoms without any medication. Some patients find that mild neuropathic pain is relieved by nonsteroidal anti-

inflammatory agents such as ibuprofen at doses of 600-800mg 2 or 3 times daily.

When pain or other dysesthetic symptoms begin to limit functional ability, tricyclic antidepressants may be useful. For predominantly nocturnal pain, oral amitriptyline can be started at low doses such as 10mg to 25mg at bedtime and gradually increased to 75mg. For pain occurring predominantly during the day, oral nortriptyline can be started at low doses such as 10mg 3 or 4 times daily and increased to 30mg 3 times daily. The anticholinergic side effects of these agents (dry mouth, urinary retention orthostatic hypotension, sedation) can be minimized by beginning with low doses and gradually titrating to the minimal effective dose. It may take up to 2 or 3 weeks for a beneficial effect to occur. Caution should be exercised with patients who have HIV dementia, as such agents may precipitate acute delirium in these cases. If one tricyclic is not effective, another might be. Thus, patients failing to respond to amitriptyline should still be given a trial of nortriptyline.

Where tricyclics are not effective, second-line choices include mexiletine, an oral analog of the local anesthetics. Gastrointestinal symptoms, dizziness and tremors are the most common dose-limiting side effects of this drug. Other agents which have been tried in the management of neuropathic pain include carbamazepine, phenytoin, baclofen and clonazepan, but experience with each is limited. The topical agent capsaicin has also been tried, but the transient increase in pain caused by the release of substance P has been so poorly tolerated that most patients are unable to complete an adequate course of it.

For patients with more severe neuropathic pain which inhibits walking, narcotic analgesics may be necessary. Useful agents include methadone, sustained-release morphine sulfate and transdermal fentanyl patches. Like the tricyclics, these agents are titrated to the minimum effective dose required for analgesia. Average daily doses for severe neuropathic pain are methadone 60mg to 80mg per day (given as 20mg 3 or 4 times daily), or transdermal fentanyl given as 25mg to 100mg ever other day. Patients should be evaluated frequently for side effects and for **ineffective** symptom control. In general, patients should be maintained on a fixed dose of medication, and a strictly "as needed" schedule should be avoided. The co-administration of tricyclic agents may allow for lower doses of narcotic, even in patients who failed them as monotherapeutic agents. Rapid development of tolerance should be anticipated in individuals with a history of substance abuse.

While some may express concern over the potential for narcotics addiction in patients receiving them chronically, many studies have shown that the proportion of patients with chronic pain who actually develop addiction is quite low. The proportion is much higher in patients with a history of substance abuse, however. Therefore, clinician the should set clear guidelines for prescribing patterns and should communicate these to patients (Table 3).[4]

Table 3. Guidelines for Narcotics Use in Patients With HIV Neuropathy and History or Suspected History of Substance Abuse.

- Use only after non-narcotic therapies have failed.
- Anticipate rapid tolerance and drug-seeking behavior in those with prior history of substance abuse.

- Prescribing Caveats:
  - Single practitioner prescribes medications.
  - "Lost" prescriptions are not refilled.
  - Narcotic prescriptions should be carefully rationed.
  - Medications should be prescribed regularly, not p.r.n. (as needed).
- For intermittent inadequate control, patient may take a set number (e.g., 4 or 6) of "rescue doses" during the month.
- Patients should be seen monthly for assessment of symptom control, side effects and prescription renewal.
- Physician response to patient hoarding or selling medications, escalation dose in uncontrolled fashion, or acquiring drugs form other physicians should be tapering and discontinuation of narcotics.

(Note: modified from Portenoy RK, *Drug Therapy*, Jan 1993).[4]

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Peripheral neuropathy

Definition

The term **peripheral neuropathy** encompasses a wide range of disorders in which the nerves outside of the brain and spinal cord--**peripheral** nerves--have been damaged. **Peripheral neuropathy** may also be referred to as **peripheral** neuritis, or if many nerves are involved, the terms polyneuropathy or polyneuritis may be used.

Description

Peripheral neuropathy is a widespread disorder, and there are many underlying causes. Some of these causes are common, such as diabetes, and others are extremely rare, such as acrylamide **poisoning** and certain inherited disorders. The most common worldwide cause of **peripheral neuropathy** is **leprosy**. Leprosy is caused by the bacterium *Mycobacterium leprae*, which attacks the **peripheral** nerves of affected people. According to statistics gathered by the World Health Organization, an estimated 1.15 million peoplehave leprosy worldwide.

Leprosy is extremely rare in the United States, where diabetes is the most commonly known cause of **peripheral neuropathy**. It has been estimated that more than 17 million people in the United States and Europe have diabetes-related polyneuropathy. Many neuropathies are idiopathic, meaning that **no** known cause can be found. The most common of the inherited **peripheral** neuropathies in the United States is **Charcot-Marie-Tooth disease**, which affects approximately 125,000 persons.

Another of the better known **peripheral** neuropathies is **Guillain-Barré syndrome**, which arises from complications associated with viral illnesses, such as cytomegalovirus, Epstein-Barr virus, and human **immunodeficiency** virus (HIV), or bacterial infection, including *Campylobacter jejuni* and **Lyme disease**. The worldwide

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incidence rate is approximately 1.7 cases per 100,000 people annually. Other well-known causes of **peripheral** neuropathies include chronic **alcoholism**, infection of the varicella-zoster virus, **botulism**, and poliomyelitis. **Peripheral neuropathy** may develop as a primary symptom, or it may be due to another disease. For example, **peripheral neuropathy** is only one symptom of diseases such as amyloid **neuropathy**, certain cancers, or inherited neurologic disorders. Such diseases may affect the **peripheral** nervous system (PNS) and the central nervous system (CNS), as well as other body tissues.

To understand **peripheral neuropathy** and its underlying causes, it may be helpful to review the structures and arrangement of the PNS.

Nerve cells and nerves

Interactive

Nerve cells are the basic building block of the nervous system. In the PNS, nerve cells can be threadlike--their width is microscopic, but their length can be measured in feet. The long, spidery extensions of nerve cells are called axons. When a nerve cell is stimulated, by touch or **pain**, for example, the message is carried along the axon, and neurotransmitters are released within the cell. Neurotransmitters are chemicals within the nervous system that direct nerve cell communication.

Certain nerve cell axons, such as the ones in the PNS, are covered with a substance called myelin. The myelin sheath may be compared to the plastic coating on electrical wires--it is there both to protect the cells and to prevent interference with the signals being transmitted. Protection is also given by Schwann cells, special cells within the nervous system that wrap around both myelinated and unmyelinated axons. The effect is similar to beads threaded on a necklace.

Nerve cell axons leading to the same areas of the body may be bundled together into nerves. Continuing the comparison to electrical wires, nerves may be compared to an electrical cord--the individual components are coated in their own sheaths and then encased together inside a larger protective covering.

Peripheral nervous system

The nervous system is classified into two parts: the CNS and the PNS. The CNS is made up of the brain and the spinal cord, and the PNS is composed of the nerves that lead to or branch off from the CNS.

The **peripheral** nerves handle a diverse array of functions in the body. This diversity is reflected in the major divisions of the PNS--the afferent and the efferent divisions. The afferent division is in charge of sending sensory information from the body to the CNS. When afferent nerve cell endings, called receptors, are stimulated, they release neurotransmitters. These neurotransmitters relay a signal to the brain, which interprets it and reacts by releasing other neurotransmitters.

Some of the neurotransmitters released by the brain are directed at the efferent division of the PNS. The efferent nerves control voluntary movements, such as moving the arms and legs, and involuntary movements, such as making the heart pump blood. The nerves controlling voluntary movements are called motor nerves, and the nerves controlling involuntary actions are referred to as autonomic nerves. The afferent and efferent divisions continually interact with each other. For example, if a person were to touch a hot stove, the receptors in the skin would transmit a message of heat and pain through the sensory nerves to the brain. The message would be processed in the brain and a reaction, such as pulling back the hand, would be transmitted via a motor nerve.

Neuropathy

NERVE DAMAGE

When an individual has a **peripheral neuropathy**, nerves of the PNS have been damaged. Nerve damage can arise from a number of causes, such as disease, physical injury, poisoning, or **malnutrition**. These agents may affect either afferent or efferent nerves. Depending on the cause of damage, the nerve cell axon, its protective myelin sheath, or both may be injured or destroyed.

CLASSIFICATION

There are hundreds of **peripheral** neuropathies. Reflecting the scope of PNS activity, symptoms may involve sensory, motor, or autonomic functions. To aid in diagnosis and **treatment**, the symptoms are classified into principal neuropathic syndromes based on the type of affected nerves and how long symptoms have been developing. Acute development refers to symptoms that have appeared within days, and subacute refers to those that have evolved over a number of weeks. Early chronic symptoms are those that take months to a few years to develop, and late chronic symptoms have been present for several years.

The classification system is composed of six principal neuropathic syndromes, which are subdivided into more specific categories. By narrowing down the possible diagnoses in this way, specific medical tests can be used more efficiently and effectively. The six syndromes and a few associated causes are listed below:

- Acute motor **paralysis**, accompanied by variable problems with sensory and autonomic functions. Neuropathies associated with this syndrome are mainly accompanied by motor nerve problems, but the sensory and autonomic nerves may also be involved. Associated disorders include Guillain-Barré syndrome, diphtheritic polyneuropathy, and porphyritic **neuropathy**.

- Subacute sensorimotor paralysis. The term sensorimotor refers to neuropathies that are mainly characterized by sensory symptoms, but also have a minor component of motor nerve problems. Poisoning with heavy metals (e.g., lead, mercury, and arsenic), chemicals, or drugs are linked to this syndrome. Diabetes, Lyme disease, and malnutrition are also possible causes.

- Chronic sensorimotor paralysis. Physical symptoms may resemble those in the above syndrome, but the time scale of symptom development is extended. This syndrome encompasses neuropathies arising from cancers, diabetes, leprosy, inherited neurologic and metabolic disorders, and **hypothyroidism**.

- **Neuropathy** associated with mitochondrial diseases. Mitochondria are organelles--structures within cells--responsible for handling a cell's energy requirements. If the mitochondria are damaged or destroyed, the cell's energy requirements are not met and it can die.

- Recurrent or relapsing polyneuropathy. This syndrome covers neuropathies that affect several nerves and may come and go, such as Guillain-Barré syndrome, porphyria, and chronic inflammatory demyelinating polyneuropathy.

- Mononeuropathy or plexopathy. Nerve damage associated with this syndrome is limited to a single nerve or a few closely associated nerves. Neuropathies related to physical injury to the nerve, such as **carpal tunnel syndrome** and **sciatica**, are included in this syndrome.

Causes and symptoms

Typical symptoms of **neuropathy** are related to the type of affected nerve. If a sensory nerve is damaged, common symptoms include numbness, tingling in the area, a prickling sensation, or pain. Pain associated with **neuropathy** can be quite intense and may be described as cutting, stabbing, crushing, or burning. In some cases, a nonpainful stimulus

may be perceived as excruciating or pain may be felt even in the absence of a stimulus. Damage to a motor nerve is usually indicated by weakness in the affected area. If the problem with the motor nerve has continued over a length of time, muscle shrinkage (atrophy) or lack of muscle tone may be noticeable. Autonomic nerve damage is most noticeable when an individual stands upright and experiences problems such as light-headedness or changes in blood pressure. Other indicators of autonomic nerve damage are lack of sweat, tears, and saliva; **constipation**; urinary retention; and **impotence**. In some cases, heart beat irregularities and respiratory problems can develop.

Symptoms may appear over days, weeks, months, or years. Their duration and the ultimate outcome of the **neuropathy** are linked to the cause of the nerve damage. Potential causes include diseases, physical injuries, poisoning, and malnutrition or alcohol abuse. In some cases, **neuropathy** is not the primary disorder, but a symptom of an underlying disease.

Disease

Diseases that cause **peripheral** neuropathies may either be acquired or inherited; in some cases, it is difficult to make that distinction. The diabetes-**peripheral neuropathy** link has been well established. A typical pattern of diabetes-associated neuropathic symptoms includes sensory effects that first begin in the feet. The associated pain or pins-and-needles, burning, crawling, or prickling sensations form a typical "stocking" distribution in the feet and lower legs. Other diabetic neuropathies affect the autonomic nerves and have potentially fatal cardiovascular complications.

Several other metabolic diseases have a strong association with **peripheral neuropathy**. Uremia, or **chronic kidney failure**, carries a 10-90% risk of eventually developing **neuropathy**, and there may be an association between liver failure and **peripheral neuropathy**. Accumulation of lipids inside blood vessels (**atherosclerosis**) can choke-off blood supply to certain **peripheral** nerves. Without oxygen and nutrients, the nerves slowly die. Mild polyneuropathy may develop in persons with low thyroid hormone levels. Individuals with abnormally enlarged skeletal extremities (acromegaly), caused by an overabundance of growth hormone, may also develop mild polyneuropathy.

Neuropathy can also result from severe vasculitides, a group of disorders in which blood vessels are inflamed. When the blood vessels are inflamed or damaged, blood supply to the nerve can be affected, injuring the nerve.

Both viral and bacterial infections have been implicated in **peripheral neuropathy**. Leprosy is caused by the bacteria *M. leprae*, which directly attack sensory nerves. Other bacterial illness may set the stage for an immune-mediated attack on the nerves. For example, one theory about Guillain-Barré syndrome involves complications following infection with *Campylobacter jejuni*, a bacterium commonly associated with **food poisoning**. This bacterium carries a protein that closely resembles components of myelin. The immune system launches an attack against the bacteria; but, according to the theory, the immune system confuses the myelin with the bacteria in some cases and attacks the myelin sheath as well. The underlying cause of **neuropathy** associated with Lyme disease is unknown; the bacteria may either promote an immune-mediated attack on the nerve or inflict damage directly.

Infection with certain viruses is associated with extremely painful sensory neuropathies. A primary example of such a **neuropathy** is caused by **shingles**. After a case of **chickenpox**, the causative virus, varicella-zoster virus, becomes inactive in sensory nerves. Years later, the virus may be reactivated. Once reactivated, it attacks and destroys axons. Infection with HIV is also associated with **peripheral neuropathy**, but the type of **neuropathy** that develops can vary. Some HIV-linked neuropathies are noted for myelin destruction rather than axonal degradation. Also, HIV infection is frequently accompanied by other infections, both bacterial and viral, that are associated with **neuropathy**.

Several types of **peripheral** neuropathies are associated with inherited disorders. These inherited disorders may primarily involve the nervous system, or the effects on the nervous system may be secondary to an inherited metabolic disorder. Inherited neuropathies can fall into several of the principal syndromes, because symptoms may be sensory, motor, or autonomic. The inheritance patterns also vary, depending on the specific disorder. The development of inherited disorders is typically drawn out over several years and may herald a degenerative condition--that is, a condition that becomes progressively worse over time. Even among specific disorders, there may be a degree of variability in inheritance patterns and symptoms. For example, Charcot-Marie-Tooth disease is usually inherited as an autosomal dominant disorder, but it can be autosomal recessive or, in rare cases, linked to the X chromosome. Its estimated frequency is approximately one in 2,500 people. Age of onset and sensory nerve involvement can vary between cases. The main symptom is a degeneration of the motor nerves in legs and arms, and resultant muscle atrophy. Other inherited neuropathies have a distinctly metabolic component. For example, in familial amyloid polyneuropathies, protein components that make up the myelin are constructed and deposited incorrectly.

Physical injury

Accidental falls and mishaps during sports and recreational activities are common causes of physical injuries that can result in **peripheral neuropathy**. The common types of injuries in these situations occur from placing too much pressure on the nerve, exceeding the nerve's capacity to stretch, blocking adequate blood supply of oxygen and nutrients to the nerve, and tearing the nerve. Pain may not always be immediately noticeable, and obvious signs of damage may take a while to develop.

These injuries usually affect one nerve or a group of closely associated nerves. For example, a common injury encountered in contact sports such as football is the "burner," or "stinger," syndrome. Typically, a stinger is caused by overstretching the main nerves that span from the neck into the arm. Immediate symptoms are numbness, tingling, and pain that travels down the arm, lasting only a minute or two. A single incident of a stinger is not dangerous, but recurrences can eventually cause permanent motor and sensory loss.

Poisoning

The poisons, or toxins, that cause **peripheral neuropathy** include drugs, industrial chemicals, and environmental toxins. **Neuropathy** that is caused by drugs usually involves sensory nerves on both sides of the body, particularly in the hands and feet, and pain is a common symptom. **Neuropathy** is an unusual side effect of medications; therefore, most people can use these drugs safely. A few of the drugs that have been linked with **peripheral neuropathy** include metronidazole, an antibiotic; phenytoin, an anticonvulsant; and simvastatin, a cholesterol-lowering medication.

Certain industrial chemicals have been shown to be poisonous to nerves (neurotoxic) following work-related exposures. Chemicals such as acrylamide, allyl chloride, and carbon disulfide have all been strongly linked to development of **peripheral neuropathy**. Organic compounds, such as N-hexane and toluene, are also encountered in work-related settings, as well as in glue-sniffing and solvent abuse. Either route of exposure can produce severe sensorimotor **neuropathy** that develops rapidly.

Heavy metals are the third group of toxins that cause **peripheral neuropathy**. Lead, arsenic, thallium, and mercury usually are not toxic in their elemental form, but rather as components in organic or inorganic compounds. The types of metal-induced neuropathies vary widely. Arsenic poisoning may mimic Guillain-Barré syndrome; lead affects motor nerves more than sensory nerves; thallium produces painful sensorimotor **neuropathy**; and the effects of mercury are seen in both the CNS and PNS.

Malnutrition and alcohol abuse

Burning, stabbing pains and numbness in the feet, and sometimes in the hands, are distinguishing features of alcoholic **neuropathy**. The level of alcohol consumption associated with this variety of **peripheral neuropathy** has been estimated as approximately 3 L of beer or 300 mL of liquor daily for three years. However, it is unclear whether alcohol alone is responsible for the neuropathic symptoms, because chronic alcoholism is strongly associated with malnutrition.

Malnutrition refers to an extreme lack of nutrients in the diet. It is unknown precisely which nutrient deficiencies cause **peripheral** neuropathies in alcoholics and famine and **starvation** patients, but it is suspected that the B **vitamins** have a significant role. For example, thiamine (vitamin B_1) deficiency is the cause of **beriberi**, a neuropathic disease characterized by **heart failure** and painful polyneuropathy of sensory nerves. **Vitamin E deficiency** seems to have a role in both CNS and PNS **neuropathy**.

Diagnosis

Clinical symptoms can indicate **peripheral neuropathy**, but an exact diagnosis requires a combination of medical history, medical tests, and possibly a process of exclusion. Certain symptoms can suggest a diagnosis, but more information is commonly needed. For example, painful, burning feet may be a symptom of alcohol abuse, diabetes, HIV infection, or an underlying malignant tumor, among other causes. Without further details, **effective treatment** would be difficult.

During a **physical examination**, an individual is asked to describe the symptoms very carefully. Detailed information about the location, nature, and duration of symptoms can help exclude some causes or even pinpoint the actual problem. The person's medical history may also provide clues as to the cause, because certain diseases and medications are linked to specific **peripheral** neuropathies. A medical history should also include information about diseases that run in the family, because some **peripheral** neuropathies are genetically linked. Information about hobbies, recreational activities, alcohol consumption, and work place activities can uncover possible injuries or exposures to poisonous substances.

The physical examination also includes blood tests, such as those that check levels of glucose and creatinine to detect diabetes and kidney problems, respectively. A **blood count** is also done to determine levels of different blood cell types. Iron, vitamin B_{12}, and other factors may be measured as well, to rule out malnutrition. More specific tests, such as an assay for heavy metals or poisonous substances, or tests to detect **vasculitis**, are not typically done unless there is reason to suspect a particular cause.

An individual with **neuropathy** may be sent to a doctor that specializes in nervous system disorders (neurologist). By considering the results of the physical examination and observations of the referring doctor, the neurologist may be able to narrow down the possible diagnoses. Additional tests, such as nerve conduction studies and **electromyography**, which tests muscle reactions, can confirm that nerve damage has occurred and may also be able to indicate the nature of the damage. For example, some neuropathies are characterized by destruction of the myelin. This type of damage is shown by slowed nerve conduction. If the axon itself has suffered damage, the nerve conduction may be slowed, but it will also be diminished in strength. Electromyography adds further information by measuring nerve conduction and muscle response, which determines whether the symptoms are due to a **neuropathy** or to a muscle disorder.

In approximately 10% of **peripheral neuropathy** cases, a nerve biopsy may be helpful. In this test, a small part of the nerve is surgically removed and examined under a microscope. This procedure is usually the most helpful in confirming a suspected diagnosis, rather than as a diagnostic procedure by itself.

Treatment

Treat the cause

Attacking the underlying cause of the **neuropathy** can prevent further nerve damage and may allow for a better recovery. For example, in cases of bacterial infection such as leprosy or Lyme disease, **antibiotics** may be given to destroy the infectious bacteria. Viral infections are more difficult to treat, because antibiotics are not **effective** against them. Neuropathies associated with drugs, chemicals, and toxins are treated in part by stopping exposure to the damaging agent. Chemicals such as ethylenediaminetetraacetic acid (EDTA) are used to help the body concentrate and excrete some toxins. Diabetic neuropathies may be treated by gaining better control of blood sugar levels, but chronic kidney failure may require dialysis or even kidney transplant to prevent or reduce nerve damage. In some cases, such as compression injury or tumors, surgery may be considered to relieve pressure on a nerve.

In a crisis situation, as in the onset of Guillain-Barré syndrome, plasma exchange, intravenous immunoglobulin, and steroids may be given. Intubation, in which a tube is inserted into the trachea to maintain an open airway, and ventilation may be required to support the respiratory system. **Treatment** may focus more on symptom management than on combating the underlying cause, at least until a definitive diagnosis has been made.

Supportive care and long-term therapy

Some **peripheral** neuropathies cannot be resolved or require time for resolution. In these cases, long-term monitoring and supportive care is necessary. Medical tests may be repeated to chart the progress of the **neuropathy**. If autonomic nerve involvement is a concern, regular monitoring of the cardiovascular system may be carried out.

Because pain is associated with many of the neuropathies, a **pain management** plan may need to be mapped out, especially if the pain becomes chronic. As in any chronic disease, narcotics are best avoided. Agents that may be helpful in neuropathic pain include amitriptyline, carbamazepine, and capsaicin cream. Physical therapy and physician-directed exercises can help maintain or improve function. In cases in which motor nerves are affected, braces and other supportive equipment can aid an individual's ability to move about.

Prognosis

The outcome for **peripheral neuropathy** depends heavily on the cause. **Peripheral neuropathy** ranges from a reversible problem to a potentially fatal complication. In the best cases, a damaged nerve regenerates. Nerve cells cannot be replaced if they are killed, but they are capable of recovering from damage. The extent of recovery is tied to the extent of the damage and a person's age and general health status. Recovery can take weeks to years, because neurons grow very slowly. Full recovery may not be possible and it may also not be possible to determine the prognosis at the outset.

If the **neuropathy** is a degenerative condition, such as Charcot-Marie-Tooth disease, an individual's condition will become worse. There may be periods of time when the disease seems to reach a plateau, but cures have not yet been discovered for many of these degenerative diseases. Therefore, continued symptoms, potentially worsening to disabilities are to be expected.

A few **peripheral** neuropathies are eventually fatal. Fatalities have been associated with some cases of **diphtheria**, botulism, and others. Some diseases associated with **neuropathy** may also be fatal, but the ultimate cause of **death** is not necessarily related to the **neuropathy**, such as with **cancer**.

Prevention

Peripheral neuropathies are preventable only to the extent that the underlying causes are preventable. Steps that a person can take to prevent potential problems include vaccines against diseases that cause **neuropathy**, such as **polio** and diphtheria. **Treatment** for physical injuries in a timely manner can help prevent permanent or worsening damage to nerves. Precautions when using certain chemicals and drugs are well advised in order to prevent exposure to neurotoxic agents. Control of chronic diseases such as diabetes may also reduce the chances of developing **peripheral neuropathy**.

Although not a preventive measure, genetic screening can serve as an early warning for potential problems. Genetic screening is available for some inherited conditions, but not all. In some cases, presence of a particular gene may not mean that a person will necessarily develop the disease, because there may be environmental and other components involved.

Key Terms

Afferent
Refers to **peripheral** nerves that transmit signals to the spinal cord and the brain. These nerves carry out sensory function.

Autonomic
Refers to **peripheral** nerves that carry signals from the brain and that control involuntary actions in the body, such as the beating of the heart.

Autosomal dominant or autosomal recessive
Refers to the inheritance pattern of a gene on a chromosome other than X or Y. Genes are inherited in pairs--one gene from each parent. However, the inheritance may not be equal, and one gene may overshadow the other in determining the final form of the encoded characteristic. The gene that overshadows the other is called the dominant gene; the overshadowed gene is the recessive one.

Axon
A long, threadlike projection that is part of a nerve cell.

Central nervous system (CNS)
The part of the nervous system that includes the brain and the spinal cord.

Efferent
Refers to **peripheral** nerves that carry signals away from the brain and spinal cord. These nerves carry out motor and autonomic functions.

Electromyography
A medical test that assesses nerve signals and muscle reactions. It can determine if there is a disorder with the nerve or if the muscle is not capable of responding.

Inheritance pattern
Refers to dominant or recessive inheritance.

Motor
Refers to **peripheral** nerves that control voluntary movements, such as moving the arms and legs.

Myelin
The protective coating on axons.

Nerve biopsy
A medical test in which a small portion of a damaged nerve is surgically removed and examined under a microscope.

Nerve conduction
The speed and strength of a signal being transmitted by nerve cells. Testing these factors can reveal the nature of nerve injury, such as damage to nerve cells or to the protective myelin sheath.

Neurotransmitter
Chemicals within the nervous system that transmit information from or between nerve cells.

Peripheral nervous system (PNS)
Nerves that are outside of the brain and spinal cord.

Sensory
Refers to **peripheral** nerves that transmit information from the senses to the brain.

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Organizations

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- Myelin Project Headquarters. Suite 225, 2001 Pennsylvania Ave., N.W., Washington, D.C. 20006-1850. (202) 452-8994. http://www.myelin.org
- **Neuropathy** Association. 60 E. 42nd St., Suite 942, New York, NY 10165. (800) 247-6968. http://www.**neuropathy**.org/association.html

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Introduction to Peripheral Neuropathy

What is Peripheral Neuropathy?

One of the very important functions of peripheral nerve cells is to alert a person to tissue injury and noxious stimuli or events in their environment. Normally, pain is a signal of imminent or actual harm to the body that initiates protective reflexes to prevent or minimize that danger. When tissue damage occurs, the resulting pain prompts special attention to the affected area and the person responds either by removing the source of danger (e.g. pulling a hand away from a hot object) or by initiating treatment quickly. This pain which is felt in response to a harmful stimulus is known as nociceptive pain. It is caused by stimulation of certain pain receptors and is generally described as sharp, aching, or throbbing. It is also the type of pain felt in some chronic, painful conditions (e.g., arthritis).

However, when pain occurs in the absence of dangerous stimuli, does not prompt protective reflexes, nor does it subside when the danger is past or when the injury has healed, it is said to be maladaptive or dysfunctional and is called neuropathic pain. It may or may not be triggered by an injury and can persist for years or decades. It is often described as burning, electric, tingling and/or shooting pain and can be continuous or intermittent. The nervous system malfunctions and becomes the cause of the pain. This type of pain serves no protective or biological function. Symptoms of neuropathic pain tend to predominate in the peripheral limbs - in the feet more than in the hands - but can also appear in different locations (e.g. cranial nerve as trigeminal neuralgia).

Peripheral neuropathy (PN) is a disorder of the peripheral nerves resulting from damage due to trauma, underlying disease, or unknown reasons (idiopathic peripheral neuropathy). The symptoms depend upon the specific types of nerves that are involved:

- Damage to a sensory nerve can produce symptoms such as pain, numbness, tingling, burning, or a loss of sensation or feeling. The pain

usually begins in the hands or feet and progresses towards the trunk of the body. Lack of sensation can cause other complications relating to recurrent injuries that may go unnoticed, (e.g., awareness of cuts or burns to the skin) and can lead to ulcers, or poor healing of wounds.

- Damage to a motor nerve results in decreased movement or control of muscles. Since movement is important for the health of many organ systems, (e.g., it promotes increased blood circulation) damage to motor function can also lead to changes in muscle, bone, skin, and other organs. Symptoms of damage to peripheral motor nerves usually begin as weakness or heaviness of the hands and/or feet and may deteriorate over time.

- Damage to peripheral nerves that link to the autonomic nervous system, which effects involuntary body systems or organs, can result in:

    - Impaired ability to regulate body temperature
    - Blurred vision
    - Reduced sweating
    - Dizziness
    - Bowel/bladder dysfunction
    - Sexual dysfunction

The neuronal damage in peripheral neuropathy is most frequently found either in:

- Small fibers - small myelinated and unmyelinated fibers are affected. It is the most common type of peripheral neuropathy in people above the age of 50. It is often unrecognized by physicians and an underlying cause for this type of peripheral neuropathy is found in less than 10% of patients. Small fiber PN is very painful to the point of being debilitating and responds slowly to medication if at all. Symptoms are many and include burning, stabbing, lancinating (piercing) pain.

- Large fibers - long fibers are myelinated and are associated with functions such as:

    - Motor function
    - Vibration perception
    - Positional sense
    - Perception of cold

Peripheral neuropathy can affect both small and large nerve fibers. The affected small fibers cause pain, and the affected large fibers cause symptoms such as reduced muscle reflex and reduced proprioception (sensory awareness of the body). Diagnosis and determination of etiology occurs in only

up to 30% of patients.

The incidence of peripheral neuropathy is not known with any degree of certainty. It has been estimated that more than 2-3 million Americans have some form of PN. The prevalence of peripheral neuropathy worldwide has been estimated to range from 2% to 8% of the population. Peripheral neuropathy affects both genders at all ages but symptoms are unique to each individual in terms of frequency, quality, and severity of pain. Peripheral neuropathy can significantly impact an individual's quality of life and daily activities by causing major disruptions including:

- Sleep disturbances
- Mood changes
- Impairment of social, occupational, and recreational functioning

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Introduction to Peripheral Neuropathy

Risk Factors for Peripheral Neuropathy

A risk factor is anything that increases a person's chances of getting a particular disease. Risk factors for peripheral neuropathy (PN) include:

- Diabetes
  - peripheral neuropathy occurs in up-to 50% of patients with diabetes (Type 1 or Type II)
  - risk of PN increases in diabetics who have difficulty controlling their levels of blood sugar
- Autoimmune Diseases
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - Guillain-Barre syndrome
- Metabolic Diseases
  - hypothyroidism
  - amyloidosis
  - vitamin B deficiency
- Hereditary Disorders
  - Charcot-Marie-Tooth disease
  - Dejerine-Sottas syndrome
- Infectious Diseases
  - Lyme disease
  - HIV/AIDS
  - Hepatitis B
  - Leprosy
- Alcohol abuse

- Stress from repetitive motion
- Vitamin deficiency (especially vitamin B)
- Chronic kidney or liver failure
- Trauma or compression of a nerve
- Paraneoplastic disorders (tumors)
- Chemotherapy drugs used for cancer treatment, including:
    - vincristine
    - cisplatin
    - taxanes
- Exposure to toxic substances
- Ischemic (circulatory) disorders

The frequency, intensity, and quality or duration of the pain in peripheral neuropathy may be determined, in part, by the underlying cause of the neuropathy as well as individual variability.

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Introduction to Peripheral Neuropathy

Classification of Peripheral Neuropathy

There are several different types of peripheral neuropathy (PN) that can be classified by the type of nerves involved. The pathways affected by nerve damage determine the distribution of pain in peripheral neuropathy. These include:

Mononeuropathy

This condition is characterized by involvement of a single peripheral nerve. This is most likely to be the result of repetitive motion stress that puts pressure on a nerve.

Mononeuropathy multiplex

In mononeuropathy multiplex, there is random involvement of multiple nerves, either serially or simultaneously, and is associated with diabetic *amyotrophy* (a type of neuropathy with pain, weakness and/or wasting of the muscles), *sarcoidosis* (An inflammation of the lymph nodes or other organs), or Lyme disease. It is often related to disturbances in the vascular system (e.g., may be seen in diabetes) which affects the nerves that those blood vessels supply.

Radiculopathy

This involvement of the nerve roots in the spine (e.g. pinched nerve).

Polyneuropathy

Polyneuropathy affects both sides of the body, more commonly legs than the arms, and symptoms usually appear first in the toes and soles of the feet. It the most common type of peripheral neuropathy and is associated with diabetes, alcoholism, vitamin B deficiencies or HIV. *Sensory peripheral neuropathy* is the most common type of polyneuropathy and is associated with

numbness, tingling, and burning. It is also associated with diabetic neuropathy, idiopathic small fiber sensory neuropathy, neuropathy associated with connective tissue disease, inherited neuropathies, HIV related neuropathy, cancer and/or chemotherapy related neuropathies. The symptoms of sensory peripheral neuropathy can be intermittent or continuous and can significantly interfere with quality of life.

There are several types of polyneuropathy, including *acute* and *chronic* polyneuropathy.

Acute Polyneuropathy

This type of polyneuropathy progresses rapidly. Approximately half of the patients have a history of respiratory or gastrointestinal infection within the 2-3 weeks prior to onset. The most common form is Guillain-Barre syndrome.

Chronic (distal) Polyneuropathy -

This is the most common type of polyneuropathy and may develop over a period of months or years. It can involve large and/or small fibers and can affect sensory, motor, and/or autonomic pathways. Some of the types of chronic polyneuropathy include:

- Chronic Demyelinating Polyneuropathy

Demyelination refers to the destruction and loss of myelin from the sheath surrounding the axon and affects both near and far segments of the nerve. It is characterized by progressive weakness and impaired sensory function in the legs and arms. It is more common in males than females and in young adults. It is closely related to Guillain-Barre syndrome. This condition is either genetic or may be acquired through inflammatory or immunological conditions (chronic inflammatory demyelinating polyneuropathy).

- Chronic Axonal Polyneuropathy

This is the most common polyneuropathy and is associated with many conditions including diabetes, nutritional deficiencies (e.g. vitamin B12), cancer, and alcohol abuse. The most common cause is diabetes.

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Introduction to Peripheral Neuropathy

Progression of Peripheral Neuropathy

Symptoms of peripheral neuropathy (PN) usually begin gradually and may barely be noticeable when they first appear. Initial sensations may be intermittent and can include tingling, numbness, or other feelings in the feet/toes or hands/fingers. Symptoms usually progress from the periphery towards the center of the body. Some individuals experience intensification of their symptoms at night.

Skin may become increasingly sensitive and the slightest touch can cause excruciating pain. Many people have pain or burning distributed in the pattern of wearing an invisible sock or glove. The pain or sensations can increase in frequency and duration and can also change in quality to include new symptoms. Each individual can have a unique pattern of pain progression.

If motor nerves are involved, the individual may experience weakness in the legs or arms and a sense of heaviness when trying to lift them. This also effects balance and increases the danger of falling and fracture. If autonomic nerves are involved, the individual may progress to having related symptoms (e.g., bowel or bladder problems, impotence, cardiac symptoms and/or reduced sweating).

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Introduction to Peripheral Neuropathy

Diabetic Neuropathy

Diabetes (type I and type II) is the most common cause of peripheral neuropathy (PN) in Western countries. The cause of diabetic neuropathy is not completely understood but some researchers theorize that the metabolic consequences of insulin deficiency and hyperglycemia are related to the initial damage of the nerve fibers and vascular insufficiency, which is common in diabetes, and may accelerate the neuropathic injury.

Peripheral neuropathy is one of the most common long-term complications of diabetes. Estimates of incidence vary widely and range from approximately 10% of diabetic patients to close to 90%. It occurs equally among Type I and Type II diabetics and has more of an effect on the quality of life of diabetic patients than other aspects of the condition (e.g. dietary restriction). The number of people affected by diabetic neuropathy increases with age since it can develop several years after the onset of diabetes. It is important to distinguish the origin of the symptoms of peripheral neuropathy in the diabetic patient since up to 10% of diabetics may have signs of peripheral neuropathy from nondiabetic causes. Progression of diabetic neuropathy is thought to be closely related to controlling the level of glucose in the blood (glycemic control).

Diabetic neuropathy accounts for more diabetes related hospitalizations than any other complication. The greatest danger associated with diabetic neuropathy is foot ulceration which can lead to the onset of gangrene and may require subsequent amputation. The presence of neuropathy significantly increases the risk of amputation. By some estimates, diabetic neuropathy is responsible for up to 75% of non-trauma related amputations among diabetics.

Diabetic neuropathy is associated with Type I and Type II diabetes although the progression is different. In Type I diabetes, typically there is a rapid deterioration of nerve function soon after onset and then it slows down,

whereas, in Type II diabetes, the nerve damage and symptoms of neuropathy are present at diagnosis and progress thereafter at a steady rate.

Diabetic neuropathy can occur in the somatic or autonomic parts of the peripheral nervous system. Nearly 50% of diabetic patients may have symptoms of autonomic peripheral neuropathy which can be mild but, nevertheless, potentially life threatening. Symptoms associated with cardiac disease, (e.g., silent cardiac ischemia, orthostatic hypotension) can be fatal or can cause significant morbidity. Cardiac disease accounts for up to 25% of deaths of diabetic patients over a 10 year time period from the time of diagnosis and is an independent risk factor for stroke.

Types of Diabetic Neuropathy

- *Focal neuropathy* - This occurs in older adults with diabetes and is usually characterized by intense acute pain which resolves within 6-8 weeks. This category includes mononeuropathy, radiculopathy, and entrapment syndromes (e.g. carpal tunnel syndrome) which occur approximately three times as often in the diabetic population.

- *Distal symmetric polyneuropathy* - This is the most commonly recognized form of diabetic neuropathy. It can involve small and/or large fibers and often commences with the beginning of insulin therapy for diabetes or with stress. It may manifest as sensory or motor neuropathy. Small nerve fiber dysfunction often occurs quite early in diabetes with symptoms of pain and exaggerated reactivity to touch (hyperalgesia).

Distal symmetric polyneuropathy can be further subdivided into *small nerve fiber* and *large nerve fiber* involvement.

Small Fiber Neuropathy

Small fiber pain is not well understood. It is thought that hyperglycemia may play a role in the increased sensitivity to pain caused by the damage of these fibers. Diabetic neuropathy seems to progress as these fibers (c-fibers) are damaged and sensitivity to pain is affected, causing pain of various intensity and severity. When the situation becomes chronic, there is no longer need for a stimulus to cause the pain, it is always present. Eventually, the fibers may die at which time the patient may no longer experience pain and may experience numbness.

Large Fiber Neuropathy

Large nerve fibers are myelinated and are associated with functions such as motor function, perception of vibration, sense of position, and perception of cold. Symptoms of large fiber neuropathy may be mild to severe and include:

- Impaired sense of vibration
- Dull pain in the bones of the lower leg or foot
- 'Hot foot' due to increased blood flow
- Shortened Achilles tendon

Most cases of diabetic neuropathy are a mixture of large and small fiber damage. Many patients experience the "glove or stocking" distribution of pain in the legs as an early sign of sensory loss.

Although some pain in diabetic neuropathy may resolve on its own, if the pain persists for more than 3 months, it is less likely to disappear. While symptoms from large fiber involvement (e.g., weakness, poor coordination) affect daily activities and may make a person more prone to falling, the effects of small fiber damage are more debilitating and significantly affect the overall wellbeing of the person since the pain be very intense, frequent, and/or last a long time.

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Introduction to Peripheral Neuropathy

Cancer Chemotherapy and Peripheral Neuropathy

Peripheral neuropathy (PN) is a disorder associated with several types of cancer and is thought to affect as many as 5% of cancer patients. Some neuropathies are caused by the cancer itself (e.g., the spread of cancer to the nervous system or compression of a tumor on a nerve) but most cases of peripheral neuropathy are caused by side effects of the drugs used for chemotherapy, many of which are neurotoxic (toxic to nerve cells). It is often difficult to determine if the malignancy is the primary cause of peripheral neuropathy or the chemotherapy.

Toxic chemotherapeutic agents interfere with the metabolic needs of the nerve cells which may lead to degeneration or injury to the axon and can affect sensory, motor and/or autonomic neurons. Symptoms may begin in a more central part of the body (e.g., the sciatic nerve) and, as more damage occurs to myelinated and unmyelinated nerve fibers, may be felt more peripherally or symptoms may begin in the peripheral limbs and progress towards the center.

Neurotoxic chemotherapeutic agents include:

- Antimitotic drugs (interfere with cell growth and/or reproduction of cancer cells), Examples of these types of drugs include:
    - plant alkaloids (e.g., vinorelbine, vincristine) - this is part of a class of drugs which causes paresthesias (abnormal sensations; tingling) in the hands and feet of up to 60% of patients. It also may cause gait disturbances and muscle weakness. This class of drugs is considered to be the least neurotoxic of the chemotherapeutic agents.
    - taxanes (e.g., paclitaxel, docetaxel) - this class of drugs may cause degeneration and reduced myelination of the axon. It can also affect autonomic cardiovascular function (e.g., blood pressure).

Symptoms may include burning, dysesthesia (unpleasant sensation), or paresthesia. Sensory loss from docetaxel is seen in up to 50% of patients and appears in some patients after the first dose. Many patients recover from the neuropathy over a long period of time. When combined with platinum-based drugs, a high percentage of patients develop sensory-motor neuropathy.

- thalidomide - this drug causes axonal neuropathy which results in sensory more than motor neuropathy. Its effects on the nervous system are long lasting and while some patients recover slowly while others do not recover at all.

- Platinum-based drugs (e.g., cisplatin, oxaliplatin, or carboplatin)- these drugs interfere with the DNA in the cancer cells which leads to their destruction. They also affect large fiber nerves and are highly associated with neurotoxic symptoms, including sensory neuropathy. It is estimated that up to 60% of patients receiving platinum-based medications suffer from PN and in many of these patients, symptoms persist beyond the treatment period. The neuropathic side effect can be a factor in limiting the dosage given for treatment.

- Interferons - these drugs boost the immune system and are used to treat certain types of cancers. Interferons have been reported to cause axonal neuropathy in some people.

Other symptoms associated with cancer chemotherapy include:

- Burning
- Painful numbness
- Allodynia (pain due to a stimulus which does not usually cause pain, e.g., light touch)
- Acroparesthesia (tingling/numbness in legs is distributed in the pattern of a glove). This is often the earliest and most persistent symptom.
- Muscle weakness
- Hypoflexia - (diminished muscle reflexes)
- Autonomic symptoms such as:
  - postural hypotension - the drop of blood pressure with postural or positional change is one of the most common manifestations of autonomic involvement
  - cardiac irregularities
  - bladder/bowel dysfunction

Most neuropathies caused by chemotherapy relate to sensory peripheral neuropathy, although damage to the small nerve fibers can also affect autonomic systems and cause associated symptoms (e.g., postural

hypotension). Some neuropathies are dose related and may appear after the first dose while others may appear following several doses of medication and may even develop after chemotherapy has been stopped since damage to the nerves is gradual.

Recovering from chemotherapy-related PN can be very slow and symptoms may be more intense during the recovery period. Regenerating nerves can cause cramping and paresthesias that are severe and interfere with daily activities. Patients who had previous nerve damage are at highest risk for developing chemotherapy-related peripheral neuropathy. As cancer treatment evolves with the use of higher doses of drugs and combinations of increasingly potent drugs, the number of cases of chemotherapy-related PN is expected to increase.

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Diagnosis of Peripheral Neuropathy

Signs and Symptoms of Peripheral Neuropathy

The signs and symptoms of peripheral neuropathy (PN) vary widely and are subject to differences among affected individuals. The pain of peripheral neuropathy has been described in many ways, including burning, lancinating, electric, and shooting. These sensations can be divided into two categories of neuropathic pain: *positive* symptoms and *negative* symptoms.

- Positive symptoms - pain associated with the neuropathy
    - spontaneous pain - pain that is independent of any stimulus, (e.g., burning, stabbing, stinging, freezing, aching, feeling of "broken glass", and/or pins and needles) Many patients experience different types of pain simultaneously (e.g., burning pain as well as shooting or stabbing pain)
    - stimulus-evoked - pain that is experienced in response to an event (e.g., pinprick or finger pressure on a particular spot)
- Negative symptoms - these are associated with a loss of function and include:
    - anesthesia - absence of pain when it should be felt (e.g., if there is an injury), numbness
    - paresthesia - abnormal sensation
    - tremor
    - gait imbalance

Additional symptoms or sensations of peripheral neuropathy include:

- Weakness, loss of grip strength, decreased manual dexterity
- Muscle atrophy (wasting)
- Loss of reflexes
- Anhidrosis (absence of sweating)
- Orthostatic hypotension (drop in blood pressure upon sitting up or

standing)

All of these sensations may occur simultaneously, intermittently, or on a constant basis and are associated with significant individual variation. Many patients with peripheral neuropathy also complain of fatigue, mood swings, difficulty with memory, and loss of coordination/balance.

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Treatment Options for Peripheral Neuropathy

Goals of Treatment for Peripheral Neuropathy

The primary goals of treatment for peripheral neuropathy include:

- Establishing and treating the underlying cause of PN when identification is possible
- Relieving peripheral nerve pain regardless of cause
- Maintaining overall function of affected parts of the body
- Preserving the patient's quality of life

Most therapies that are effective for neuropathic pain are not specific to the cause or type of the neuropathy and may be helpful for other types of neuropathy.

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Treatment Options for Peripheral Neuropathy

Treating the Underlying Cause of Peripheral Neuropathy

The treatment plan for peripheral neuropathy (PN) is determined by the diagnosis. Thus, the first step is to try to determine the underlying cause of the neuropathy. If a reversible or treatable cause of the neuropathy is identified, such as a metabolic, hormonal, or infectious disorder, then the appropriate measures are taken to treat the disorder and prevent any further nerve damage. Vitamin supplementation is prescribed for those patients with a known specific vitamin deficiency and splinting or modifications are made for those patients whose neuropathy is related to a repetitive motion disorder such as carpal tunnel syndrome. For patients with diabetic neuropathy, control of blood sugar levels is a mainstay of treatment.

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Treatment Options for Peripheral Neuropathy

Management of Symptoms of Peripheral Neuropathy

If the cause of the peripheral neuropathy (PN) cannot be determined or if the underlying cause of the neuropathy cannot be resolved, therapy focuses on reducing the symptoms. There is not one adequate, predictable, and specific treatment to control established neuropathic pain. However, there are a variety of medications available to help control the pain. Not all medications are effective for all persons. Some of the medications may take several weeks to reach their maximal potential. Therefore, attainment of adequate pain control requires a good working relationship with the health care team as well as time and patience.

The overall aim of treatment is to relieve pain while maximizing comfort and function, and to help the individual cope with their (often chronic) situation.

Currently, there are no standard guidelines available for the treatment of peripheral neuropathy. Clinical trials have not proven to be conclusive in terms of identifying effective treatments for several reasons including:

- Medications are considered effective even if only a small number of subjects experience limited pain relief.
- People with PN want pain relief without side effects from the medication which is unrealistic. Since results from clinical trials often involve subjective evaluation of a treatment efficacy, results are not very accurate or reliable.
- The response to placebo ("sugar pill") treatment in clinical trials is significant and can be seen in up to 30-50% of patients.

Most clinicians consider successful treatment to result in a 30-50% reduction in pain, which is usually significantly less than patient expectations.

In an effort to control neuropathic pain, clinicians use a variety of modalities, including:

- Drug therapy
- Physical and/or occupational therapy
- Surgical therapy

Drug Therapy

In general, drug therapy for peripheral neuropathy is individualized for each patient and depends upon a number of factors that your doctor will take into consideration based upon your past and present medical history, extent of pain, other medications that you may be taking, presence of other serious comorbid conditions (e.g., kidney disease, liver disease, etc...) and history of drug allergies. Many of the drugs used to treat peripheral neuropathy are considered "off-label", meaning that they are approved by the FDA for the treatment of other specific conditions but are also prescribed for the treatment of peripheral neuropathy. More recently, two newer drugs [pregabalin (Lyrica) and duloxetine (Cymbalta)] have received FDA approval for the treatment of neuropathic pain associated with diabetic neuropathy.

The major classes of drugs currently used to treat peripheral neuropathy include:

- Antidepressants
- Anticonvulsants
- Antiarrhythmics
- Narcotic analgesics
- Non-narcotic analgesics
- Other drugs
- Topical agents

Antidepressants

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are the most widely studied class of drugs regarding treatment for neuropathic pain. Examples include:

- Amitriplyline (Elavil)
- Nortriptylene (Aventyl)
- Desipramine (Norpramine)
- Imipramine (Janimine)

Tricyclic antidepressants work by blocking the reuptake of serotonin (a neurotransmitter related to pain) and noradrenaline and are thought to relieve pain by inhibiting or modifying the sodium channels of the cells involved in sensation of pain. They are generally considered effective for:

- Spontaneous pain
- Hyperalgesia

There is evidence that the efficacy of different TCAs is similar but that individuals may respond slightly better to one drug over the others. If patient response is not sufficient with one TCA, the physicians may prescribe a different TCA until one is found be effective for the individual. In studies evaluating the use of these drugs for diabetic neuropathy, approximately one-third of patients achieved a 50% reduction of pain.

Efficacy of TCAs does not appear to be related to the quality of the pain (e.g. stabbing, or burning).

Side-effects of TCAs can be strong and their overall tolerability is considered poor although they are widely used. Side-effects may outweigh the benefits especially for older people. Adverse effects may include:

- Dry mouth
- Dizziness
- Constipation
- Drowsiness/sedation
- Muscle twitches
- Weakness
- Nausea
- Weight gain
- Urinary retention
- Cognitive/memory difficulties
- Increased sweating
- Decreased libido (sexual drive)

TCAs are contraindicated in people with various health conditions including:

- Cardiac arrhythmias (irregular heartbeat)
- Recent heart attack
- Congestive heart failure
- Glaucoma

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are drugs that block the reuptake of serotonin - a natural hormone that is involved in the transmission of nerve impulses. Clinical trials indicate that they are less effective than TCAs for controlling pain for patients with PN. For patients who cannot tolerate TCAs, SSRIs may be considered an option.

Examples of SSRI's include:

- Citalopram (Celexa)
- Paroxetine (Paxil)
- Fluoxetine (Prozac)
- Sertraline (Zoloft)

Adverse effects of SSRI's may include:

- Somnolence or insomnia
- Nausea/vomiting
- Dry mouth
- Decreased libido and/or impotence

Atypical Antidepressants

Atypical antidepressants are a class of drugs that work by inhibiting the reuptake of serotonin and norepinephrine. Examples include:

- Duloxetine (Cymbalta) - Approved by the FDA in September 2004, duloxetine (Cymbalta) was the first drug that was specifically approved for the treatment of neuropathic pain associated with diabetic neuropathy. Two randomized, controlled clinical trials of Cymbalta demonstrated the safety and efficacy of this drug for the management of neuropathic pain in patients with diabetic neuropathy. The most common side-effects reported by patients included:
    - nausea
    - somnolence (sleepiness)
    - dizziness - some patients also experienced "hot flashes" together with dizziness
    - reduced appetite
    - constipation
- Venlafaxine (Effexor) - Venlafaxine has fewer side effects than TCAs. There is some indication that it may be effective for cancer-related neuropathies. There is now an extended release form of venlafaxine which appears to be effective for diabetic peripheral neuropathy. Adverse reactions may include:
    - nausea
    - dizziness
    - fatigue
    - sexual dysfunction
    - dry mouth
- Bupropion - Some studies indicate that this drug diminishes pain by approximately 30% in some individuals. It is considered to be better tolerated than TCAs. The sustained release form of bupropion was the subject of a clinical trial with patients suffering from several types of

neuropathic pain. Approximately 70% of the subjects reported significant pain relief after two weeks with a 30% reduction of pain scores as well as improved quality of life measures. Adverse effects may include:

- restlessness
- agitation
- anxiety
- insomnia
- skin rash
- aching muscles
- frequent urination
- weight gain or weight loss

Anticonvulsants

Anticonvulsant drugs inhibit the sodium channels at the cellular level to stabilize the cell membranes. This process appears to have the effect of reducing neuropathic pain.

- Gabapentin (Neurontin) - This drug is a popular first-line treatment for neuropathic pain although the mode of action of this drug is not clear. Some studies involving patients with at diabetic neuropathy show significant improvement in pain scores as well as secondary outcomes (e.g., mood, sleep disturbances) while other studies did not yield such definitive results. Results for peripheral neuropathy are also not uniformly conclusive. Side effects, most commonly dizziness or drowsiness, are considered to be tolerable and better than for many other medications used to treat peripheral neuropathy. In order to minimize sedation or drowsiness, many patients take the larger portion of their daily dose at night before bedtime.

- Pregabalin (Lyrica) - Pregabalin is a new anticonvulsant drug for peripheral neuropathic pain that was approved by the U.S. Food and Drug Administration (FDA) in August 2005. It is also a Schedule V controlled substance. Pregabalin is closely related in both chemical structure and pharamcological action to gabapentin. Pregabalin is indicated for the treatment of neuropathic pain associated with diabetic neuropathy and for the treatment of neuropathic pain associated with post-herpetic neuralgia. Randomized, controlled clinical trials have shown that pregabalin was safe and effective in decreasing neuropathic pain in patients with diabetic neuropathy and also improved mood, sleep disturbances, and overall quality of life. The most common side-effects experienced by patients in clinical trials who were treated with pregabalin included dizziness, somnolence (sleepiness), peripheral edema (swelling of the limbs), and weight gain. Because pregabalin is a Schedule V controlled substance, patients must be carefully monitored to prevent the

potential for drug dependency and abuse.

- Lamotrigine (Lamictal) - This is a newer anticonvulsant. Some studies indicate moderate relief for pain related to diabetic neuropathy and HIV related neuropathy. Side effects are considered minimal and may include:
    - dizziness
    - headache
    - ataxia (loss of coordination)
    - fatigue
    - nausea
    - blurred vision
    - skin rash (mild to severe)
- Carbamazepine (Tegretol) - This drug has been approved by the FDA for the treatment of trigeminal neuralgia. There is limited data regarding its efficacy for the treatment of peripheral neuropathy. Side effects are frequent and can be very pronounced in the elderly. They include:
    - dizziness
    - ausea/vomiting
    - confusion
    - blurred vision
    - Fatigue
    - liver dysfunction
    - leucopenia (reduction in the number of white blood cells)
- Oxcarbazepine (Trileptal) is an analog of carbamazepine and is usually better tolerated. This drug is usually used for the treatment of epilepsy. Limited data from small trials indicate that it may improve pain scores for people suffering from diabetic neuropathy.

- Phenytoin (Dilantin) is an anticonvulsant drug that is used for the treatment of epilepsy. Phenytoin is usually not used as a first line medication for PN since results from studies are inconsistent. There are some indications that it may be more effective when given intravenously for painful neuropathies. Phenytoin also inhibits insulin production which could be problematic for diabetic patients.

- Topiramate (Topamax) is an anticonvulsant medication that has been reported to be effective in relieving pain associated with various neuropathies, including diabetic neuropathy, in case reports and small clinical trials.

Antiarrhythmic Drugs

- Mexiletine - Some studies indicate that mexiletine (Mexitil) is effective for

painful diabetic neuropathy but results from other studies are conflicting. Side effects may include:

- nausea/vomiting
- dizziness
- tremor
- headache
- abnormal liver function

Narcotic Analgesics

- Oxycodone - This drug is a narcotic and, therefore, subject to drug dependence. Oxycodone is effective for some types of neuralgia (e.g., postherpetic neuralgia) but data is limited regarding sensory neuropathy. The controlled release form of oxycodone has shown promising results for diabetic neuropathy with significant improvement in pain level and sleep quality. The extended-release formulation of oxycodone is preferred for long-term therapy. Doses are titrated slowly until pain relief is achieved. Higher doses of oxycodone yield significant results for patients with peripheral neuropathy, however, they are also associated with more adverse effects. Side-effects are common and include:

  - nausea/vomiting
  - decreased appetite
  - constipation
  - dry mouth
  - dizziness
  - fatigue
  - increased sweating
  - decreased sex drive
  - muscle twitches
  - seizures
  - changes in breathing
  - allergic reactions

Oxycodone is contraindicated in people with a history of drug/alcohol abuse or patients with chronic obstructive pulmonary disease.

- Levorphanol - Limited data indicates modest pain relief for some types of neuropathic pain (less efficacy for sensory neuropathy than for other types such as postherpetic neuraligia) but side effects occur frequently and include:

  - itching
  - mood swings
  - confusion

- weakness

Non-Narcotic Analgesics

- Tramadol - This drug has properties of narcotics but does not bind to opioid receptors so is less likely to cause dependence or abuse. It has been in use in the US since 1995. Limited trials indicate that its effect is similar to TCAs or levorphanol for diabetic and other types of neuropathies. Pain relief was significant and overall health and quality of life scores improved. Small studies indicated that this effect may still be seen after 6 months. Some studies reported improvement in spontaneous pain, touch-evoked pain, and allodynia. Adverse effects are frequent, mild, and considered tolerable. They include:

  - nausea and/or constipation
  - headache
  - somnolence (fatigue, sleepiness)

Tramadol appears to be better tolerated than TCAs. It is contraindicated for people with hypersensitivity to opiates, a history of alcohol or drug use, or liver/kidney disease.

Mild neuropathic pain may be alleviated by a variety of analgesics available "over-the-counter" such as aspirin, acetaminophen (e.g., Tylenol), or ibuprofen (e.g., Advil; Motrin).

Dextromethorphan

Dextromethorphan is commonly used as a non-prescription cough suppressant. Studies in a limited number of patients indicate a significant improvement in pain scores for patients with diabetic neuropathy who were treated with Dextromethorphan . Side effects may include:

- Sedation (up to 70% of patients)
- Memory impairment
- Ataxia (reduced motor coordination)

Topical Agents

- Capsaicin - This topical agent is extracted from chili peppers and depletes substance P from sensory nerves in the skin. Results for neuropathic pain are inconsistent. Efficacy for diabetic neuropathy may be moderate (some report up to 90% reduction on pain scores) with improvement seen in other quality of life parameters including work, sleep, and daily functioning.

There are indications that capsaicin is as effective as amitriptyline for reducing pain and improving the quality of life for patients with diabetic neuropathy but without systemic side effects.

Capsaicin is available over-the-counter at a strength of 0.075%. The most common side effect is burning or pain when first administered but this subsides over time. It is important not to rub your eyes after administering capsaicin since contact with the eyes will cause considerable burning and could cause eye damage. Some people have reported, coughing, sneezing, or respiratory irritation due to the residue or fumes that remain following the application of capsaicin. These symptoms can be minimized by applying capsaicin in a well ventilated room.

- Topical lidocaine - This drug is available as a patch and is approved by the FDA for treatment of postherpetic neuralgia. It appears to be less effective for other neuropathic pain which usually extends over an area much larger than the size of the patch. It may be beneficial for placement at sites of particularly intense pain.

Nerve Block

A nerve block involves the injection of a drug (such as steroids, opioids, or local anesthetics) directly into the area of an affected nerve in an attempt to interrupt the transmission of pain signals to the brain. Although some patients with peripheral neuropathy report relief from pain following a nerve block, most studies indicate that the therapeutic value of the injections is short-lived.

Summary of Drug Therapy Recommendations

To date, there have been no formal standard guidelines regarding drug therapy for peripheral neuropathy. The conclusions of an article appearing in 2003 in the *New England Journal of Medicine* (Volume 348; pp. 1243-1255, March 26, 2003) were as follows:

- Gabapentin is a reasonable first-choice for efficacy and tolerability
- If there is no pain relief or if it is insufficient at the maximum dose, adding a second drug, such as Tramadol, is a reasonable choice, beginning at a low dose and raising the dose slowly.
- If the individual cannot tolerate gabapentin, the initial drug of choice is Tramadol.
- If pain persists, adding a third drug, such as oxcarbazepine, which is as effective and better tolerated than tricyclic antidepressants, is a reasonable choice, starting at a low dose and then slowly increasing the dose.
- If a combination of three drugs is ineffective, one may wish to try the extended release formulation of a narcotic analgesic, preferably

sustained release oral morphine.

Capsaicin can be used at any time since it has no systemic side effects. Some people have found it to be helpful when used in conjunction with prescribed medications.

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Treatment Options for Peripheral Neuropathy

Treatment for Cancer-Related Peripheral Neuropathy

Treatment is similar to that of non-cancer related PN. Gabapentin is considered to be the treatment of choice. TCAs and SSRIs are not as effective or well tolerated. Carbamazepine may be beneficial but its hepatic and hematological side effects make it less desirable for cancer patients. Data regarding oxcarbazepine is very limited. Lamotrigine has shown promise with indications that a good number of patients respond favorable. It also has the advantage of no hepatic side effects and the rash (if it occurs) is considered tolerable. Capsaicin can be used at any time.

Massage and stretching help alleviate cramps and some benefit is seen from quinine found either in tonic water or over-the-counter preparations. An effort should be made to keep the dose as low as possible due to potential hematological side effects (e.g., hemolysis, thrombocytopenia).

Education and counseling of the patient with chemotherapy-induced PN is very important since they could be experiencing a chronic long-term change of daily functioning. Two areas that can directly impact this adjustment include physical and occupational therapy as discussed above.

Neuroprotective Agents

In addition to the medications and therapies used for treatment of chemotherapy-related PN, researchers are investigating drugs that are able to prevent the nerve damage from occurring altogether. These drugs are called *neuroprotective agents*.

Neuroprotective agents work in two ways:

- They protect the nerve cells from the toxic effects of chemotherapy
- They promote regeneration of nerve cells without promoting tumor growth.

These drugs include:

- Thiol drugs containing sulfur
- Lipoic acid (comes as an oral supplement which has been used in Europe)
- Amifostine - may be particularly effective for prevention of PN from platinum-based drugs. This drug was approved by the FDA for reducing renal toxicity during the administration of cisplatin and may also have neuroprotective properties.

Neurotrophic Agents

Neurotrophic agents or nerve growth factors (NGF) work by ensuring the survival of neurons. Limited studies have shown that NGF decreases or disappears after administration of chemotherapy. Some clinical trials have shown that patients with diabetic neuropathy and HIV induced neuropathy exhibited improved function of small-fiber sensory nerves and reduction of pain intensity following administration of rhNGF. Trials are ongoing.

Pyrimidine isaxonine - this drug shows properties for enhancing regeneration of peripheral nerves but has side effects including hepatic toxicity which presently limits its clinical use.

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Treatment Options for Peripheral Neuropathy

Treatment for Cancer-Related Peripheral Neuropathy

Treatment is similar to that of non-cancer related PN. Gabapentin is considered to be the treatment of choice. TCAs and SSRIs are not as effective or well tolerated. Carbamazepine may be beneficial but its hepatic and hematological side effects make it less desirable for cancer patients. Data regarding oxcarbazepine is very limited. Lamotrigine has shown promise with indications that a good number of patients respond favorable. It also has the advantage of no hepatic side effects and the rash (if it occurs) is considered tolerable. Capsaicin can be used at any time.

Massage and stretching help alleviate cramps and some benefit is seen from quinine found either in tonic water or over-the-counter preparations. An effort should be made to keep the dose as low as possible due to potential hematological side effects (e.g., hemolysis, thrombocytopenia).

Education and counseling of the patient with chemotherapy-induced PN is very important since they could be experiencing a chronic long-term change of daily functioning. Two areas that can directly impact this adjustment include physical and occupational therapy as discussed above.

Neuroprotective Agents

In addition to the medications and therapies used for treatment of chemotherapy-related PN, researchers are investigating drugs that are able to prevent the nerve damage from occurring altogether. These drugs are called *neuroprotective agents*.

Neuroprotective agents work in two ways:

- They protect the nerve cells from the toxic effects of chemotherapy
- They promote regeneration of nerve cells without promoting tumor growth.

These drugs include:

- Thiol drugs containing sulfur
- Lipoic acid (comes as an oral supplement which has been used in Europe)
- Amifostine - may be particularly effective for prevention of PN from platinum-based drugs. This drug was approved by the FDA for reducing renal toxicity during the administration of cisplatin and may also have neuroprotective properties.

Neurotrophic Agents

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1: Eur J Cancer. 2006 Jan;42(1):24-30. Epub 2005 Nov 15. Related Articles, Links
ELSEVIER FULL-TEXT ARTICLE

Peripheral neuropathy: a persisting challenge in paclitaxel-based regimes.

Mielke S, Sparreboom A, Mross K.

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Cumulative peripheral neuropathy (PNP) still remains a limitation to optimal treatment with paclitaxel (PAC), especially in more dose-dense schedules. This primary sensory PNP may affect the majority of patients after administration of certain cumulative dosages of PAC, while the exact mechanisms of PAC-induced PNP are not known. While a number of preclinical models revealed its vehicle Cremophor EL (CrEL) to be mainly responsible for ganglionopathy, axonopathy and demyelination, clinical data also supports a strong and independent effect of PAC itself, which is most likely based on disturbances in the microtubules in perikaryons, axons and glia cells. Indeed, clinical trials of CrEL-free formulations of PAC still report grade III neurotoxicity as dose-limiting. As treatment options of PAC-induced PNP are rare the use of specific scoring systems for screening purposes is strongly encouraged. In this report we review and discuss the pathogenesis, incidence, risk factors, diagnosis, pharmacodynamics and treatment options for PAC-induced PNP.

Publication Types:
- Review

PMID: 16293411 [PubMed - indexed for MEDLINE]

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1: Semin Oncol. 2006 Feb;33(1):15-49. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy.

Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F.

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fred.hausheer@bnpi.com

Peripheral neuropathy induced by cancer chemotherapy represents a large unmet need for patients due to the absence of treatment that can prevent or mitigate this common clinical problem. Chemotherapy-induced peripheral neuropathy (CIPN) diagnosis and management is further compounded by the lack of reliable and standardized means to diagnose and monitor patients who are at risk for, or who are symptomatic from, this complication of treatment. The pathogenesis and pathophysiology of CIPN are not fully elucidated, but there is increasing evidence of damage or interference with tubulin function. The diagnosis of CIPN may present a diagnostic dilemma due to the large number of potential toxic etiologies and conditions, which may mimic some of the clinical features; the diagnosis must be approached with care in such patients. The incidence and severity of CIPN is commonly under-reported by physicians as compared with patients. The development of new and reliable methods for the assessment of CIPN as well as safe and effective treatments to prevent this complication of treatment would represent important medical advancements for cancer patients.

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1: Am J Geriatr Pharmacother. 2005 Dec;3(4):274-87.

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ELSEVIER FULL-TEXT ARTICLE

Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin?

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OBJECTIVE: This article reviews the available information on pregabalin, a new anticonvulsant for peripheral neuropathic pain. Pregabalin was provisionally approved by the US Food and Drug Administration in December 2004 and was granted final approval after controlled substance scheduling (Schedule V) by the US Drug Enforcement Agency in August 2005. METHODS: A MEDLINE search (1986-August 2005) was conducted to identify pertinent studies in the English language. The search terms included pregabalin, PD144723, CI-1008, gabapentin, and neuropathic pain. Additional references were obtained from the bibliographies of identified articles. All studies that evaluated any aspect of pregabalin in vitro or in vivo in animals or humans were included, with a focus on data relevant to older adults. RESULTS: In preclinical studies, pregabalin, a structural congener of gabapentin, exhibited antinociceptive activity in animal models of neuropathic and inflammatory pain. Unlike gabapentin, pregabalin was well absorbed (> 90%), and its absorption was dose independent. Like gabapentin, pregabalin was predominantly excreted unchanged in the urine (> or = 98%). Dosed at 50 to 200 mg TID, pregabalin was superior to placebo in relieving pain and improving sleep and health-related quality of life in patients with diabetic peripheral neuropathy and postherpetic neuralgia ($P < 0.001$-$P < 0.049$). No active-controlled trials were available. The most problematic adverse events associated with pregabalin were dizziness and somnolence (21%-26%). CONCLUSIONS: In the absence of active-controlled clinical trials and geriatric-specific efficacy/tolerability data, the place of pregabalin in the analgesic armamentarium for the elderly is unclear. Because pregabalin is a Schedule V controlled substance, its utility is not compromised by substantial limitation of access or the need for extra steps in prescribing. However, abuse potential is a consideration, and

utilization should be carefully monitored, particularly in patients with a past or current history of substance abuse. The improved pharmacokinetic profile of pregabalin relative to gabapentin is manifested in linear and dose-independent absorption and a narrow therapeutic dosing range. However, pregabalin still requires multiple administrations per day, and daily doses > 150 mg/d require dose titration. The relatively high frequency of central nervous system adverse events, particularly dizziness and somnolence, is a concern in the elderly. Time and further experience should clarify the role of this agent.

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- Review

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1: Arch Phys Med Rehabil. 2005 Mar;86(3 Suppl 1):S11-7. Related Articles, Links
ELSEVIER FULL-TEXT ARTICLE

Neuromuscular rehabilitation and electrodiagnosis. 2. Peripheral neuropathy.

Weiss LD, Weiss JM, Johns JS, Strommen JA, Kim CT, Williams FH, Rashbaum IG.

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This self-directed learning module highlights peripheral neuropathies. It is part of the chapter on neuromuscular rehabilitation and electrodiagnosis in the Self-Directed Physiatric Education Program for practitioners and trainees in physical medicine and rehabilitation. This article specifically focuses on diagnostic criteria and classifications of peripheral neuropathy, including diabetic, alcoholic, carcinomatous, human immunodeficiency virus-associated, and critical illness polyneuropathies. Treatment options are reviewed. The causes for difficult to obtain nerve conduction studies are highlighted. OVERALL ARTICLE OBJECTIVE: To summarize the diagnosis, classification, and treatment of peripheral neuropathies.

PMID: 15761795 [PubMed - indexed for MEDLINE]

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Introduction to Peripheral Neuropathy

The nervous system controls the smooth functioning of all systems in the body as well as all interactions between the human being and the environment. The nervous system is comprised of millions of neurons and many interconnections that form a communications network within the body that governs many functions including:

- The five senses (sight, hearing, touch, smell, and taste)
- Voluntary functions (e.g. walking, holding an object)
- Involuntary functions (e.g. breathing, blood pressure)
- Cognitive reasoning

The human nervous system has two major components:

- Central nervous system - includes the brain and spinal cord.
- Peripheral nervous system - includes the nerves that lead from the brain and spinal cord to all parts of the body.

The extensive system of specialized nerves which comprise the peripheral nervous system is responsible for a variety of important functions:

- Motor nerves- these nerves carry messages from the brain to the body are responsible for the ability to move any part of the body (e.g., hands, feet)
- Sensory nerves - these nerves carry information from organs (e.g. the skin) to the central nervous system where it is processed into sensation (e.g., touch, temperature changes, and vibrations)
- Autonomic nerves - these nerves control autonomic (involuntary) functions including cardiac, respiratory and genitourinary systems

Each nerve cell (neuron) in the human body has three parts:

- Cell body - also called soma which is similar to the cell body of all other cells.
- Dendrites - Fibers of varying sizes which extend from the cell body and

are sensory terminals of the neuron. They receive messages from neighboring cells and transmit them to the cell body.

- Axon - a long nerve fiber (can reach up to 1 meter in length) that extends from the cell body and transfers a signal from the cell body to another nerve or muscle cell. Axons can be either myelinated (insulated by the myelin sheath made up of specialized cells) or unmyelinated which affects the speed of transmission of impulses.

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Diseases and Conditions

Peripheral neuropathy

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Overview

Peripheral neuropathy is a term used to describe disorders of your **peripheral** nervous system. Your **peripheral** nervous system includes nerves in your face, arms, legs, torso, and some nerves in your skull. In fact, all of your nerves not located in your central nervous system — which includes the brain and the spinal cord — are **peripheral** nerves.

DIABETES AND ENDOCRINE SYS

Diabetes Complications
- **Peripheral neuropathy**
- Gestational diabetes
- Type 1 diabetes
- Diabetic retinopathy
- Metabolic syndrome
- Dehydration
- Type 2 diabetes
- Prediabetes
- Diabetic coma
- Diabetic hyperosmolar syndrome
- Diabetic ketoacidosis

Neuropathies may affect just one nerve (mononeuropathy) or several nerves (polyneuropathy). Your communication between your brain and your muscles, skin, internal organs and blood vessels. When nerves can't communicate properly, and that miscommunication causes symptoms such as pain or n

Peripheral neuropathy often affects people with diabetes and autoimmune diseases such as rheum lupus. Certain vitamin deficiencies, some medications and alcoholism can also damage **peripheral** n

Treating the underlying condition may relieve some cases of **peripheral neuropathy**. In other cases, **peripheral neuropathy** may focus on managing pain. **Peripheral** nerves have a remarkable ability t themselves, and new treatments for **peripheral neuropathy** using nerve growth factors or gene ther even better chances for recovery in the future.

Signs and symptoms

Neurological symptoms may occur related to your central nervous system, which consists of your bra or your **peripheral** nervous system, which links your spinal cord and brain to all other parts of your b network of **peripheral** nerves includes the motor nerves, which help your muscles contract, and the s which allow you to feel a range of sensations. In addition, your **peripheral** nerves help control some functions of the autonomic nervous system, which regulates your internal organs, sweat glands and t

Unfortunately, **peripheral** nerves are fragile and easily damaged. Damage to a **peripheral** nerve can communication between the area it serves and your brain, affecting your ability to move certain musc sensations. Your symptoms will depend on the cause of your **neuropathy** and on which nerve or ner

If a sensory nerve is damaged, you're likely to experience symptoms that may include:

- Pain
- Numbness
- Tingling
- Muscle weakness
- Burning
- Loss of feeling

These symptoms often begin gradually. You may have a tingling sensation or numbness that starts ir balls of your feet and spreads upward. Tingling might also begin in your hands and extend up your ar cases your skin may become so sensitive that the slightest touch is agonizing. You may also have nu a complete lack of feeling, in your hands or feet.

At times your symptoms may be barely noticeable, and some people go years without realizing anyth others, symptoms are constant, and especially at night may be almost unbearable. Signs and symptc

- The sensation that you're wearing an invisible glove or sock
- Burning pain
- Sharp, jabbing or electric-like pain
- Extreme sensitivity to touch, even light touch
- Lack of coordination

If your motor nerves are affected, you may have weakness or paralysis of the muscles controlled by t if you have damage to nerves that control certain functions of the autonomic nervous system, you mi bladder problems, reduced sweating or impotence. You might also experience a sharp fall in your blo you stand up, which may cause you to faint or feel lightheaded.

Causes

A number of factors can cause neuropathies. When a **single** nerve is affected, the most likely cause type of repetitive use that puts pressure on the nerve. Nerve pressure can result from using a cast or spending a long time in an unnatural position — such as typing at a computer keyboard — or having abnormal bone growth.

When damage occurs to several nerves, the cause frequently is diabetes. At least half of all people w develop some type of **neuropathy**. Other common causes include alcoholism, HIV/AIDS, inherited di amyloidosis and a deficiency of certain vitamins, especially B vitamins.

Other causes of **peripheral** nerve damage may include:

- **Other diseases.** These include autoimmune diseases, such as lupus and rheumatoid arthriti liver disease and an underactive thyroid (hypothyroidism).
- **Exposure to poisons.** These may include some toxic substances and certain medications — used to treat cancer.
- **Genetic makeup.** You may inherit a tendency to develop **peripheral neuropathy**.
- **Bacterial or viral infections.** An acute condition called Guillain-Barre syndrome frequently c damage to all or part of your **peripheral** nerves by destroying the myelin sheath that covers n myelin sheath acts as an insulator for your nerves and helps conduct nerve impulses. Althou of Guillain-Barre syndrome isn't known, most cases occur after an infection, surgery or immur

Unfortunately, it's not always easy to pinpoint the cause of **peripheral neuropathy**. In fact, if your **ne** associated with diabetes, it's possible the cause may never be found.

- Type 1 diabetes
- Type 2 diabetes
- Rheumatoid arthritis
- Lupus
- Guillain-Barre syndrome
- Hypothyroidism
- Amyloidosis

Risk factors

Having diabetes places you at high risk of developing **peripheral** nerve damage. In fact, at least half diabetes have some form of **neuropathy**. The risk increases the longer you have diabetes, and is hig who've had the disease for more than 25 years. Your risk is even greater if you are older than 40 or h controlling your blood sugar level.

Although researchers don't understand exactly how damage occurs, a high blood sugar level seems nerves' ability to transmit signals. You can help reduce your risk by carefully following a medically ap keeping your blood sugar level as close to normal as possible.

Your risk of developing **peripheral neuropathy** is also higher if you have one or more of the followin

- **Alcohol abuse.** Excessive drinking of alcohol can affect your nervous system, causing numb hands and feet.
- **Vitamin deficiency.** A lack of certain vitamins, especially B-1 (thiamin) and B-12 makes **peri neuropathy** more likely. Pernicious anemia, which occurs when your body can't absorb B-12 leads to **peripheral neuropathy**.
- **Immune system disorders.** You're more likely to develop **peripheral neuropathy** if you hav disease, such as lupus or rheumatoid arthritis, or if your immune system is compromised by t immunodeficiency virus (HIV) or AIDS.
- **Other health problems.** Medical conditions, including certain types of cancer, kidney disease disease, also can put you at risk of nerve damage.
- **Repetitive stress.** A job or hobby that puts stress on one nerve for long periods of time incre of developing **peripheral neuropathy**. In carpal tunnel syndrome, for example, the median n through your wrist into your fingers becomes compressed. Repetitive assembly line work or w prolonged, heavy gripping can compress the median nerve. Playing golf, tennis or a musical i using vibrating power tools or even crutches also can put pressure on **peripheral** nerves.
- **Toxic substances.** Exposure to some toxic substances can make you susceptible to **periph** damage. These substances include heavy metals, such as lead, mercury and arsenic; organi certain medications, such as those used to treat cancer or AIDS.

- Alcoholism
- Vitamin deficiency anemia
- HIV/AIDS
- Carpal tunnel syndrome

When to seek medical advice

See your doctor regularly if you have diabetes, a compromised immune system or any other chronic

If you have a cut or sore on your foot that doesn't seem to be healing, is infected or is getting worse, promptly, especially if you have diabetes. Even minor sores that don't heal can turn into ulcers. In the cases, untreated foot ulcers may become gangrenous — a condition in which the tissue dies — and even amputation of your foot.

Seek medical care right away if you notice any unusual tingling, weakness or pain in your hands or fe diagnosis and treatment offers the best chance for controlling your symptoms and preventing further **peripheral** nerves. If your symptoms are interfering with your sleep or you feel depressed, your doct specialist may be able to suggest treatments that can help.

Screening and diagnosis

Peripheral neuropathy isn't a **single** disease, but rather a syndrome with many causes. For that rea difficult to diagnose. To help in the diagnosis, your doctor will likely take a full medical history and per and neurological exam that may include checking your tendon reflexes, your muscle strength and ton feel certain sensations, and your posture and coordination.

Your doctor may also request blood tests to check your level of vitamin B-12, a urinalysis, thyroid fun often, electromyography (EMG) — a test that measures the electrical discharges produced in your m of this test, you'll be asked to have a nerve conduction study, which measures how quickly your nerv signals. A nerve conduction study is often used to diagnose carpal tunnel syndrome and other **peripl** disorders.

Your doctor may recommend a nerve biopsy, a procedure in which a small portion of a nerve is remo for abnormalities. But even a nerve biopsy may not always reveal what's damaging your nerves.

- Electromyography (EMG)

Complications

Diabetic **neuropathy** may cause a number of complications. Damage to the nerves in your feet, alon circulation, can lead to ulcers and even gangrene. But it's not only your feet that are vulnerable — dia **neuropathy** can affect any organ in your body.

If nerves related to digestion are damaged, for instance, your stomach may empty too slowly, which r constant nausea, vomiting and bloating. Or you may have frequent constipation or diarrhea. In some have problems with bladder control or impotence.

Other complications include:

- Partial or complete loss of movement or sensation
- Low blood pressure
- Impotence
- Depression
- Weight loss

- Constipation
- Diarrhea
- Depression

Treatment

The goal of treatment is to manage the underlying condition causing your **neuropathy** and repair dar provide symptom relief. If your doctor hasn't been able to determine the cause of your **neuropathy**, h variety of medications to see which help ease your symptoms.

Controlling a chronic condition may not eliminate your **neuropathy**, but it can play a key role in mana what your doctor may recommend for treating various underlying conditions:

- **Diabetes.** If you have diabetes, you and your doctor can work together to keep your blood su to normal as possible. Maintaining normal blood sugar levels helps protect your nerves, thouç may initially get worse before they begin to improve.
- **Vitamin deficiency.** If your **neuropathy** is the result of a vitamin deficiency, it's likely your sy improve once the deficiency is corrected. Your doctor may recommend injections of vitamin B days, then once a month. If you have pernicious anemia, you'll need regular injections for the and possibly additional vitamin supplements. You'll also need to eat a healthy diet.
- **Autoimmune disorder.** If your **neuropathy** is caused by an inflammatory or autoimmune prc will be aimed at controlling your immune response.
- **Nerve pressure.** In cases where **neuropathy** is the result of pressure on a nerve, treatment on eliminating the source of the pressure. That might mean adding ergonomic chairs, desks c your home or office, changing the way you hold tools or instruments, or taking a break from c sports. In some cases of nerve compression, you may need surgery to correct the problem.
- **Toxic substances or medications.** If toxins or medications are responsible for the **neuropat** you stop taking the medication or avoid further exposure to the toxin to prevent the **neuropatl** progressing further.

Medications

Medications can ease pain symptoms, but most have side effects, especially if you take them for lonç you take pain medication regularly, including over-the-counter (OTC) products, discuss the benefits a with your doctor. Medications that may help provide pain relief for **neuropathy** include:

- **Pain relievers.** OTC pain relievers, such as acetaminophen (Tylenol, others), and nonsteroid inflammatory drugs (NSAIDs), such as aspirin and ibuprofen (Advil, Motrin, others), usually he For more severe symptoms, your doctor may recommend prescription NSAIDs. If you take NS periods of time or in large doses, you may develop nausea, stomach pain, bleeding or even u
- **Anti-seizure medications.** Drugs such as gabapentin (Neurontin), carbamazepine (Tegretol) (Dilantin) were originally developed to treat seizure disorders (epilepsy). However, doctors oft them for jabbing pain. Side effects may include drowsiness and dizziness.
- **Lidocaine patch.** This patch contains the topical anesthetic lidocaine. You apply it to the are is most severe, and you can use up to three patches a day to relieve pain. This treatment has effects except, for some people, a rash at the site of the patch.
- **Tricyclic antidepressants.** Antidepressant medications, such as amitriptyline, nortriptyline (F desipramine (Norpramin) and imipramine (Tofranil), may provide relief for mild to moderate sy interfering with chemical processes in your brain that cause you to feel pain. Common side ef medications may include balance problems, dry mouth, nausea, tiredness, constipation and w help reduce these side effects, your doctor will likely start you off at a low dose and slowly inc of drug you take. If you're bothered by insomnia, your doctor may also recommend an antidep sleeping medication. Some studies have also suggested that selective serotonin reuptake inh such as paroxetine (Paxil) and fluoxetine hydrochloride (Prozac), may help relieve the signs a **peripheral neuropathy**.
- **Other medications.** Opioid analgesics, such as codeine or oxycodone (OxyContin) may be u pain. However, this class of medications produces numerous side effects, including addiction, term use of these drugs undesirable. Mexiletine (Mexitil), a drug ordinarily used to treat irregu sometimes helps relieve burning pain.

Research aimed at finding more **effective** treatments for **peripheral neuropathy** is ongoing. For exa are looking at developing nerve growth factors to reproduce the chemicals that signal your body to re fibers. Unfortunately, **no** medications can repair nerve damage yet, but the body can regenerate nerv substance is removed.

Therapies

Several drug-free therapies and techniques may also help with pain relief. Doctors frequently use the with medications, but some may be **effective** on their own. They include:

- **Transcutaneous electrical nerve stimulation (TENS).** Your doctor may prescribe this thera help prevent pain signals from reaching your brain. TENS delivers tiny electrical impulses to s pathways through small electrodes placed on your skin. Although safe and painless, TENS d everyone or for all types of pain.
- **Biofeedback.** This therapy uses a special machine to teach you how to control certain body r reduce pain. You then learn how to control these same responses yourself. Biofeedback tech taught in medical centers and hospitals.
- **Acupuncture.** The National Institutes of Health has found that acupuncture can be an **effecti** chronic pain, possibly including the pain of **neuropathy**. Keep in mind that you may not get in with acupuncture and may require more than one session.
- **Hypnosis.** Many adults can be hypnotized by a trained professional, but for hypnosis to be m also have to be a willing and motivated participant. During hypnosis, you'll typically receive su intended to decrease your perception of pain.
- **Relaxation techniques.** Designed to help reduce the muscle tension that makes pain worse, techniques range from deep-breathing exercises to visualization (imagining yourself floating i for example), yoga and meditation. You might want to take classes in one or more of these te can learn them yourself using books or tapes.

- Topical painkillers: Rubbing in relief
- Biofeedback: Using the power of your mind to improve your health
- Acupuncture: Sharp answers to pointed questions
- Hypnosis: An altered state of consciousness
- Relax: Techniques to help you achieve tranquility

Prevention

The best way to prevent **peripheral neuropathy** is to carefully manage any medical condition that p That means controlling your blood sugar level if you have diabetes or talking to your doctor about saf treatments if you think you may have a problem with alcohol.

Whether or not you have a medical condition, eat a healthy diet that's rich in fruits, vegetables, whole protein. The best food sources of vitamin B-12 are meats, fish, eggs, low-fat dairy foods and fortified strict vegetarian, fortified cereals are a good source of vitamin B-12 for you, but you may also want t doctor about B-12 supplements.

As much as possible, avoid repetitive motions, cramped positions and toxic chemicals, all of which m damage.

Self-care

The following suggestions can help you manage **peripheral neuropathy**:

- **Take care of your feet, especially if you have diabetes.** Check your feet daily for signs of b calluses. Tight shoes and socks can worsen pain and tingling and may lead to sores that won loose cotton socks and padded shoes. You can use a semicircular hoop, which is available in stores, to keep bedcovers off hot or sensitive feet.
- **Exercise.** Ask your doctor about an exercise routine that's right for you. Regular exercise ma **neuropathy** pain and can help control blood sugar levels.
- **Quit smoking.** Cigarette smoking can affect circulation, increasing the risk of foot problems a amputation.
- **Eat healthy meals.** If you're at high risk of **neuropathy** or have a chronic medical condition, I especially important. Emphasize low-fat meats and dairy products and include lots of fruits, ve whole grains in your diet. Drink alcohol in moderation.
- **Massage your hands and feet, or have someone massage them for you.** Massage helps

circulation, stimulates nerves and may temporarily relieve pain.
- **Avoid prolonged pressure.** Don't keep your knees crossed or lean on your elbows for long p Doing so may cause new nerve damage.

- Diabetes self-care: Strategies to reduce your risk of complications
- Massage: A relaxing way to relieve muscle tension
- Stop smoking: Strategies to help you quit

Coping skills

Living with chronic pain or disability presents daily challenges. Some of these suggestions may make to cope:

- **Set priorities.** Decide which tasks you need to do on a given day, such as paying bills or sho groceries, and which can wait until another time. Stay active, but don't overdo.
- **Get out of the house.** When you have severe pain, it's natural to want to be alone. But this o to focus on your pain. Instead, visit a friend, go to a movie or take a walk.
- **Seek and accept support.** It isn't a sign of weakness to ask for or accept help when you nee support from family and friends, consider joining a chronic pain support group. Although supp for everyone, they can be good places to hear about coping techniques or treatments that ha others. You'll also meet people who understand what you're going through. To find a support community, check with your doctor, a nurse or the county health department.
- **Prepare for challenging situations.** If something especially stressful is coming up in your lif or a new job, knowing what you have to do ahead of time can help you cope.
- **Talk to a counselor or therapist.** Insomnia, depression and impotence are possible complic **peripheral neuropathy**. If you experience any of these, you may find it helpful to talk to a cou in addition to your primary care doctor. There are treatments that can help.

November 01, 2005

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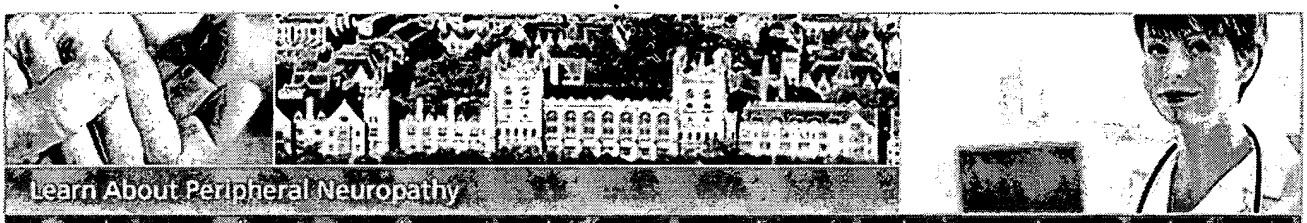

About Peripheral Neuropathy - Symptoms

What is **Peripheral** Neuropathy? | What Causes **Peripheral** Neuropathy? | Symptoms

Peripheral neuropathy usually starts with numbness, prickling or tingling in the toes or fingers. It may spread up to the feet or hands and cause burning, freezing, throbbing and/or shooting pain that is often worse at night.

The pain can be either constant or periodic, but usually the pain is felt equally on both sides of the body—in both hands or in both feet. Some types of **peripheral** neuropathy develop suddenly, while others progress more slowly over many years.

The symptoms of **peripheral** neuropathy often include:

- A sensation of wearing an invisible "glove" or "sock"
- Burning sensation or freezing pain
- Sharp, jabbing or electric-like pain
- Extreme sensitivity to touch
- Difficulty sleeping because of feet and leg pain
- Loss of balance and coordination
- Muscle weakness
- Difficulty walking or moving the arms
- Unusual sweating
- Abnormalities in blood pressure or pulse

Symptoms such as experiencing weakness or not being able to hold something, not knowing where your feet are, and experiencing pain that feels as if it is stabbing or burning in your limbs, could be signs of **peripheral** neuropathy.

The symptoms of **peripheral** neuropathy may depend on the kind of **peripheral** nerves that have been damaged.

Three types of **peripheral** nerves: sensory, motor and autonomic

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Peripheral neuropathy

Definition

The term peripheral neuropathy encompasses a wide range of disorders in which the nerves outside of the brain and spinal cord--peripheral nerves--have been damaged. Peripheral neuropathy may also be referred to as peripheral neuritis, or if many nerves are involved, the terms polyneuropathy or polyneuritis may be used.

Description

Peripheral neuropathy is a widespread disorder, and there are many underlying causes. Some of these causes are common, such as diabetes, and others are extremely rare, such as acrylamide **poisoning** and certain inherited disorders. The most common worldwide cause of peripheral neuropathy is **leprosy**. Leprosy is caused by the bacterium *Mycobacterium leprae*, which attacks the peripheral nerves of affected people. According to statistics gathered by the World Health Organization, an estimated 1.15 million peoplehave leprosy worldwide.

Leprosy is extremely rare in the United States, where diabetes is the most commonly known cause of peripheral neuropathy. It has been estimated that more than 17 million people in the United States and Europe have diabetes-related polyneuropathy. Many neuropathies are idiopathic, meaning that no known cause can be found. The most common of the inherited peripheral neuropathies in the United States is **Charcot-Marie-Tooth disease**, which affects approximately 125,000 persons.

Another of the better known peripheral neuropathies is **Guillain-Barré syndrome**, which arises from complications associated with viral illnesses, such as cytomegalovirus, Epstein-Barr virus, and human **immunodeficiency** virus (HIV), or bacterial infection, including *Campylobacter jejuni* and **Lyme disease**. The worldwide incidence rate is approximately 1.7 cases per 100,000 people annually. Other well-known causes of peripheral neuropathies include chronic **alcoholism**, infection of the varicella-zoster virus, **botulism**, and poliomyelitis. Peripheral neuropathy may develop as a primary symptom, or it may be due to another disease. For example, peripheral neuropathy is only one symptom of diseases such as amyloid neuropathy, certain cancers, or inherited neurologic disorders. Such diseases may affect the peripheral nervous system (PNS) and the central nervous system (CNS), as well as other body tissues.

To understand peripheral neuropathy and its underlying causes, it may be helpful to review the structures and arrangement of the PNS.

Nerve cells and nerves

Nerve cells are the basic building block of the nervous system. In the PNS, nerve cells can be threadlike--their width is microscopic, but their length can be measured in feet. The long, spidery extensions of nerve cells are called axons. When a nerve cell is stimulated, by touch or **pain**, for example, the message is carried along the axon, and neurotransmitters are released within the cell. Neurotransmitters are chemicals within the nervous system that direct nerve cell communication.

Certain nerve cell axons, such as the ones in the PNS, are covered with a substance

called myelin. The myelin sheath may be compared to the plastic coating on electrical wires--it is there both to protect the cells and to prevent interference with the signals being transmitted. Protection is also given by Schwann cells, special cells within the nervous system that wrap around both myelinated and unmyelinated axons. The effect is similar to beads threaded on a necklace.

Nerve cell axons leading to the same areas of the body may be bundled together into nerves. Continuing the comparison to electrical wires, nerves may be compared to an electrical cord--the individual components are coated in their own sheaths and then encased together inside a larger protective covering.

Peripheral nervous system

The nervous system is classified into two parts: the CNS and the PNS. The CNS is made up of the brain and the spinal cord, and the PNS is composed of the nerves that lead to or branch off from the CNS.

The peripheral nerves handle a diverse array of functions in the body. This diversity is reflected in the major divisions of the PNS--the afferent and the efferent divisions. The afferent division is in charge of sending sensory information from the body to the CNS. When afferent nerve cell endings, called receptors, are stimulated, they release neurotransmitters. These neurotransmitters relay a signal to the brain, which interprets it and reacts by releasing other neurotransmitters.

Some of the neurotransmitters released by the brain are directed at the efferent division of the PNS. The efferent nerves control voluntary movements, such as moving the arms and legs, and involuntary movements, such as making the heart pump blood. The nerves controlling voluntary movements are called motor nerves, and the nerves controlling involuntary actions are referred to as autonomic nerves. The afferent and efferent divisions continually interact with each other. For example, if a person were to touch a hot stove, the receptors in the skin would transmit a message of heat and pain through the sensory nerves to the brain. The message would be processed in the brain and a reaction, such as pulling back the hand, would be transmitted via a motor nerve.

Neuropathy

NERVE DAMAGE

When an individual has a peripheral neuropathy, nerves of the PNS have been damaged. Nerve damage can arise from a number of causes, such as disease, physical injury, poisoning, or **malnutrition**. These agents may affect either afferent or efferent nerves. Depending on the cause of damage, the nerve cell axon, its protective myelin sheath, or both may be injured or destroyed.

CLASSIFICATION

There are hundreds of peripheral neuropathies. Reflecting the scope of PNS activity, symptoms may involve sensory, motor, or autonomic functions. To aid in diagnosis and treatment, the symptoms are classified into principal neuropathic syndromes based on the type of affected nerves and how long symptoms have been developing. Acute development refers to symptoms that have appeared within days, and subacute refers to those that have evolved over a number of weeks. Early chronic symptoms are those that take months to a few years to develop, and late chronic symptoms have been present for several years.

The classification system is composed of six principal neuropathic syndromes, which are subdivided into more specific categories. By narrowing down the possible diagnoses in

this way, specific medical tests can be used more efficiently and effectively. The six syndromes and a few associated causes are listed below:

- Acute motor **paralysis**, accompanied by variable problems with sensory and autonomic functions. Neuropathies associated with this syndrome are mainly accompanied by motor nerve problems, but the sensory and autonomic nerves may also be involved. Associated disorders include Guillain-Barré syndrome, diphtheritic polyneuropathy, and porphyritic neuropathy.

- Subacute sensorimotor paralysis. The term sensorimotor refers to neuropathies that are mainly characterized by sensory symptoms, but also have a minor component of motor nerve problems. Poisoning with heavy metals (e.g., lead, mercury, and arsenic), chemicals, or drugs are linked to this syndrome. Diabetes, Lyme disease, and malnutrition are also possible causes.

- Chronic sensorimotor paralysis. Physical symptoms may resemble those in the above syndrome, but the time scale of symptom development is extended. This syndrome encompasses neuropathies arising from cancers, diabetes, leprosy, inherited neurologic and metabolic disorders, and **hypothyroidism**.

- Neuropathy associated with mitochondrial diseases. Mitochondria are organelles--structures within cells--responsible for handling a cell's energy requirements. If the mitochondria are damaged or destroyed, the cell's energy requirements are not met and it can die.

- Recurrent or relapsing polyneuropathy. This syndrome covers neuropathies that affect several nerves and may come and go, such as Guillain-Barré syndrome, porphyria, and chronic inflammatory demyelinating polyneuropathy.

- Mononeuropathy or plexopathy. Nerve damage associated with this syndrome is limited to a single nerve or a few closely associated nerves. Neuropathies related to physical injury to the nerve, such as **carpal tunnel syndrome** and **sciatica**, are included in this syndrome.

Causes and symptoms

Typical symptoms of neuropathy are related to the type of affected nerve. If a sensory nerve is damaged, common symptoms include numbness, tingling in the area, a prickling sensation, or pain. Pain associated with neuropathy can be quite intense and may be described as cutting, stabbing, crushing, or burning. In some cases, a nonpainful stimulus may be perceived as excruciating or pain may be felt even in the absence of a stimulus. Damage to a motor nerve is usually indicated by weakness in the affected area. If the problem with the motor nerve has continued over a length of time, muscle shrinkage (atrophy) or lack of muscle tone may be noticeable. Autonomic nerve damage is most noticeable when an individual stands upright and experiences problems such as light-headedness or changes in blood pressure. Other indicators of autonomic nerve damage are lack of sweat, tears, and saliva; **constipation**; urinary retention; and **impotence**. In some cases, heart beat irregularities and respiratory problems can develop.

Symptoms may appear over days, weeks, months, or years. Their duration and the ultimate outcome of the neuropathy are linked to the cause of the nerve damage. Potential causes include diseases, physical injuries, poisoning, and malnutrition or alcohol abuse. In some cases, neuropathy is not the primary disorder, but a symptom of an underlying disease.

Disease

Diseases that cause peripheral neuropathies may either be acquired or inherited; in some cases, it is difficult to make that distinction. The diabetes-peripheral neuropathy link has been well established. A typical pattern of diabetes-associated neuropathic symptoms includes sensory effects that first begin in the feet. The associated pain or pins-and-needles, burning, crawling, or prickling sensations form a typical "stocking" distribution in the feet and lower legs. Other diabetic neuropathies affect the autonomic nerves and have potentially fatal cardiovascular complications.

Several other metabolic diseases have a strong association with peripheral neuropathy. Uremia, or **chronic kidney failure**, carries a 10-90% risk of eventually developing neuropathy, and there may be an association between liver failure and peripheral neuropathy. Accumulation of lipids inside blood vessels (**atherosclerosis**) can choke-off blood supply to certain peripheral nerves. Without oxygen and nutrients, the nerves slowly die. Mild polyneuropathy may develop in persons with low thyroid hormone levels. Individuals with abnormally enlarged skeletal extremities (acromegaly), caused by an overabundance of growth hormone, may also develop mild polyneuropathy.

Neuropathy can also result from severe vasculitides, a group of disorders in which blood vessels are inflamed. When the blood vessels are inflamed or damaged, blood supply to the nerve can be affected, injuring the nerve.

Both viral and bacterial infections have been implicated in peripheral neuropathy. Leprosy is caused by the bacteria *M. leprae*, which directly attack sensory nerves. Other bacterial illness may set the stage for an immune-mediated attack on the nerves. For example, one theory about Guillain-Barré syndrome involves complications following infection with *Campylobacter jejuni*, a bacterium commonly associated with **food poisoning**. This bacterium carries a protein that closely resembles components of myelin. The immune system launches an attack against the bacteria; but, according to the theory, the immune system confuses the myelin with the bacteria in some cases and attacks the myelin sheath as well. The underlying cause of neuropathy associated with Lyme disease is unknown; the bacteria may either promote an immune-mediated attack on the nerve or inflict damage directly.

Infection with certain viruses is associated with extremely painful sensory neuropathies. A primary example of such a neuropathy is caused by **shingles**. After a case of **chickenpox**, the causative virus, varicella-zoster virus, becomes inactive in sensory nerves. Years later, the virus may be reactivated. Once reactivated, it attacks and destroys axons. Infection with HIV is also associated with peripheral neuropathy, but the type of neuropathy that develops can vary. Some HIV-linked neuropathies are noted for myelin destruction rather than axonal degradation. Also, HIV infection is frequently accompanied by other infections, both bacterial and viral, that are associated with neuropathy.

Several types of peripheral neuropathies are associated with inherited disorders. These inherited disorders may primarily involve the nervous system, or the effects on the nervous system may be secondary to an inherited metabolic disorder. Inherited neuropathies can fall into several of the principal syndromes, because symptoms may be sensory, motor, or autonomic. The inheritance patterns also vary, depending on the specific disorder. The development of inherited disorders is typically drawn out over several years and may herald a degenerative condition--that is, a condition that becomes progressively worse over time. Even among specific disorders, there may be a degree of variability in inheritance patterns and symptoms. For example, Charcot-Marie-Tooth disease is usually inherited as an autosomal dominant disorder, but it can be autosomal recessive or, in rare cases, linked to the X chromosome. Its estimated frequency is approximately one in 2,500 people. Age of onset and sensory nerve involvement can vary between cases. The main symptom is a degeneration of the motor nerves in legs and arms, and resultant muscle atrophy. Other inherited neuropathies have a distinctly metabolic component. For example, in familial amyloid polyneuropathies, protein components that make up the myelin are constructed and deposited incorrectly.

Physical injury

Accidental falls and mishaps during sports and recreational activities are common causes of physical injuries that can result in peripheral neuropathy. The common types of injuries in these situations occur from placing too much pressure on the nerve, exceeding the nerve's capacity to stretch, blocking adequate blood supply of oxygen and nutrients to the nerve, and tearing the nerve. Pain may not always be immediately noticeable, and obvious signs of damage may take a while to develop.

These injuries usually affect one nerve or a group of closely associated nerves. For example, a common injury encountered in contact sports such as football is the "burner," or "stinger," syndrome. Typically, a stinger is caused by overstretching the main nerves that span from the neck into the arm. Immediate symptoms are numbness, tingling, and pain that travels down the arm, lasting only a minute or two. A single incident of a stinger is not dangerous, but recurrences can eventually cause permanent motor and sensory loss.

Poisoning

The poisons, or toxins, that cause peripheral neuropathy include drugs, industrial chemicals, and environmental toxins. Neuropathy that is caused by drugs usually involves sensory nerves on both sides of the body, particularly in the hands and feet, and pain is a common symptom. Neuropathy is an unusual side effect of medications; therefore, most people can use these drugs safely. A few of the drugs that have been linked with peripheral neuropathy include metronidazole, an antibiotic; phenytoin, an anticonvulsant; and simvastatin, a cholesterol-lowering medication.

Certain industrial chemicals have been shown to be poisonous to nerves (neurotoxic) following work-related exposures. Chemicals such as acrylamide, allyl chloride, and carbon disulfide have all been strongly linked to development of peripheral neuropathy. Organic compounds, such as N-hexane and toluene, are also encountered in work-related settings, as well as in glue-sniffing and solvent abuse. Either route of exposure can produce severe sensorimotor neuropathy that develops rapidly.

Heavy metals are the third group of toxins that cause peripheral neuropathy. Lead, arsenic, thallium, and mercury usually are not toxic in their elemental form, but rather as components in organic or inorganic compounds. The types of metal-induced neuropathies vary widely. Arsenic poisoning may mimic Guillain-Barré syndrome; lead affects motor nerves more than sensory nerves; thallium produces painful sensorimotor neuropathy; and the effects of mercury are seen in both the CNS and PNS.

Malnutrition and alcohol abuse

Burning, stabbing pains and numbness in the feet, and sometimes in the hands, are distinguishing features of alcoholic neuropathy. The level of alcohol consumption associated with this variety of peripheral neuropathy has been estimated as approximately 3 L of beer or 300 mL of liquor daily for three years. However, it is unclear whether alcohol alone is responsible for the neuropathic symptoms, because chronic alcoholism is strongly associated with malnutrition.

Malnutrition refers to an extreme lack of nutrients in the diet. It is unknown precisely which nutrient deficiencies cause peripheral neuropathies in alcoholics and famine and **starvation** patients, but it is suspected that the B **vitamins** have a significant role. For example, thiamine (vitamin B_1) deficiency is the cause of **beriberi**, a neuropathic disease characterized by **heart failure** and painful polyneuropathy of sensory nerves. **Vitamin E deficiency** seems to have a role in both CNS and PNS neuropathy.

Diagnosis

Clinical symptoms can indicate peripheral neuropathy, but an exact diagnosis requires a combination of medical history, medical tests, and possibly a process of exclusion. Certain symptoms can suggest a diagnosis, but more information is commonly needed. For example, painful, burning feet may be a symptom of alcohol abuse, diabetes, HIV infection, or an underlying malignant tumor, among other causes. Without further details, effective treatment would be difficult.

During a **physical examination**, an individual is asked to describe the symptoms very carefully. Detailed information about the location, nature, and duration of symptoms can help exclude some causes or even pinpoint the actual problem. The person's medical history may also provide clues as to the cause, because certain diseases and medications are linked to specific peripheral neuropathies. A medical history should also include information about diseases that run in the family, because some peripheral neuropathies are genetically linked. Information about hobbies, recreational activities, alcohol consumption, and work place activities can uncover possible injuries or exposures to poisonous substances.

The physical examination also includes blood tests, such as those that check levels of glucose and creatinine to detect diabetes and kidney problems, respectively. A **blood count** is also done to determine levels of different blood cell types. Iron, vitamin B_{12}, and other factors may be measured as well, to rule out malnutrition. More specific tests, such as an assay for heavy metals or poisonous substances, or tests to detect **vasculitis**, are not typically done unless there is reason to suspect a particular cause.

An individual with neuropathy may be sent to a doctor that specializes in nervous system disorders (neurologist). By considering the results of the physical examination and observations of the referring doctor, the neurologist may be able to narrow down the possible diagnoses. Additional tests, such as nerve conduction studies and **electromyography**, which tests muscle reactions, can confirm that nerve damage has occurred and may also be able to indicate the nature of the damage. For example, some neuropathies are characterized by destruction of the myelin. This type of damage is shown by slowed nerve conduction. If the axon itself has suffered damage, the nerve conduction may be slowed, but it will also be diminished in strength. Electromyography adds further information by measuring nerve conduction and muscle response, which determines whether the symptoms are due to a neuropathy or to a muscle disorder.

In approximately 10% of peripheral neuropathy cases, a nerve biopsy may be helpful. In this test, a small part of the nerve is surgically removed and examined under a microscope. This procedure is usually the most helpful in confirming a suspected diagnosis, rather than as a diagnostic procedure by itself.

Treatment

Treat the cause

Attacking the underlying cause of the neuropathy can prevent further nerve damage and may allow for a better recovery. For example, in cases of bacterial infection such as leprosy or Lyme disease, **antibiotics** may be given to destroy the infectious bacteria. Viral infections are more difficult to treat, because antibiotics are not effective against them. Neuropathies associated with drugs, chemicals, and toxins are treated in part by stopping exposure to the damaging agent. Chemicals such as ethylenediaminetetraacetic acid (EDTA) are used to help the body concentrate and excrete some toxins. Diabetic neuropathies may be treated by gaining better control of blood sugar levels, but chronic kidney failure may require dialysis or even kidney transplant to prevent or reduce nerve damage. In some cases, such as compression injury or tumors, surgery may be considered to relieve pressure on a nerve.

In a crisis situation, as in the onset of Guillain-Barré syndrome, plasma exchange, intravenous immunoglobulin, and steroids may be given. Intubation, in which a tube is inserted into the trachea to maintain an open airway, and ventilation may be required to support the respiratory system. Treatment may focus more on symptom management than on combating the underlying cause, at least until a definitive diagnosis has been made.

Supportive care and long-term therapy

Some peripheral neuropathies cannot be resolved or require time for resolution. In these cases, long-term monitoring and supportive care is necessary. Medical tests may be repeated to chart the progress of the neuropathy. If autonomic nerve involvement is a concern, regular monitoring of the cardiovascular system may be carried out.

Because pain is associated with many of the neuropathies, a **pain management** plan may need to be mapped out, especially if the pain becomes chronic. As in any chronic disease, narcotics are best avoided. Agents that may be helpful in neuropathic pain include amitriptyline, carbamazepine, and capsaicin cream. Physical therapy and physician-directed exercises can help maintain or improve function. In cases in which motor nerves are affected, braces and other supportive equipment can aid an individual's ability to move about.

Prognosis

The outcome for peripheral neuropathy depends heavily on the cause. Peripheral neuropathy ranges from a reversible problem to a potentially fatal complication. In the best cases, a damaged nerve regenerates. Nerve cells cannot be replaced if they are killed, but they are capable of recovering from damage. The extent of recovery is tied to the extent of the damage and a person's age and general health status. Recovery can take weeks to years, because neurons grow very slowly. Full recovery may not be possible and it may also not be possible to determine the prognosis at the outset.

If the neuropathy is a degenerative condition, such as Charcot-Marie-Tooth disease, an individual's condition will become worse. There may be periods of time when the disease seems to reach a plateau, but cures have not yet been discovered for many of these degenerative diseases. Therefore, continued symptoms, potentially worsening to disabilities are to be expected.

A few peripheral neuropathies are eventually fatal. Fatalities have been associated with some cases of **diphtheria**, botulism, and others. Some diseases associated with neuropathy may also be fatal, but the ultimate cause of **death** is not necessarily related to the neuropathy, such as with **cancer**.

Prevention

Peripheral neuropathies are preventable only to the extent that the underlying causes are preventable. Steps that a person can take to prevent potential problems include vaccines against diseases that cause neuropathy, such as **polio** and diphtheria. Treatment for physical injuries in a timely manner can help prevent permanent or worsening damage to nerves. Precautions when using certain chemicals and drugs are well advised in order to prevent exposure to neurotoxic agents. Control of chronic diseases such as diabetes may also reduce the chances of developing peripheral neuropathy.

Although not a preventive measure, genetic screening can serve as an early warning for potential problems. Genetic screening is available for some inherited conditions, but not all. In some cases, presence of a particular gene may not mean that a person will necessarily develop the disease, because there may be environmental and other

components involved.

Key Terms

Afferent
Refers to peripheral nerves that transmit signals to the spinal cord and the brain. These nerves carry out sensory function.

Autonomic
Refers to peripheral nerves that carry signals from the brain and that control involuntary actions in the body, such as the beating of the heart.

Autosomal dominant or autosomal recessive
Refers to the inheritance pattern of a gene on a chromosome other than X or Y. Genes are inherited in pairs--one gene from each parent. However, the inheritance may not be equal, and one gene may overshadow the other in determining the final form of the encoded characteristic. The gene that overshadows the other is called the dominant gene; the overshadowed gene is the recessive one.

Axon
A long, threadlike projection that is part of a nerve cell.

Central nervous system (CNS)
The part of the nervous system that includes the brain and the spinal cord.

Efferent
Refers to peripheral nerves that carry signals away from the brain and spinal cord. These nerves carry out motor and autonomic functions.

Electromyography
A medical test that assesses nerve signals and muscle reactions. It can determine if there is a disorder with the nerve or if the muscle is not capable of responding.

Inheritance pattern
Refers to dominant or recessive inheritance.

Motor
Refers to peripheral nerves that control voluntary movements, such as moving the arms and legs.

Myelin
The protective coating on axons.

Nerve biopsy
A medical test in which a small portion of a damaged nerve is surgically removed and examined under a microscope.

Nerve conduction
The speed and strength of a signal being transmitted by nerve cells. Testing these factors can reveal the nature of nerve injury, such as damage to nerve cells or to the protective myelin sheath.

Neurotransmitter
Chemicals within the nervous system that transmit information from or

between nerve cells.

Peripheral nervous system (PNS)
Nerves that are outside of the brain and spinal cord.

Sensory
Refers to peripheral nerves that transmit information from the senses to the brain.

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Organizations

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- Neuropathy Association. 60 E. 42nd St., Suite 942, New York, NY 10165. (800) 247-6968. http://www.neuropathy.org/association.html

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Peripheral Neuropathy and HIV

By Michael J. Polydefkis, M.D.

Peripheral nerve damage is one of the most common neurological complications of HIV infection and its treatment. Of these, the distal sensory neuropathies, which occur in the advanced stages of HIV disease, are the most common, affecting approximately 30% of AIDS patients. It is important, however, to recognize that other forms of **peripheral** nerve disease occur in HIV infection. Many are caused by other infectious agents and are therefore potentially treatable. This article will briefly review less common forms of **peripheral** nerve injury in HIV and will then focus on the HIV associated sensory neuropathies.

[Return to top]

Peripheral Neuropathies other than HIV Associated Sensory Neuropathies

In the early phase of HIV disease, patients may develop acute or chronic inflammatory demyelinating **neuropathy** (AIDP, CIDP). AIDP, also known as Guillain Barré syndrome (GBS), can be the initial manifestation of HIV infection and is indistinguishable clinically and electrophysiologically from that seen in uninfected patients. One feature of HIV-associated AIDP is a mononuclear CSF pleocytosis accompanying elevated CSP. This contrasts with non-HIV GBS in which there are

typically **no** cells in spinal fluid. The precise epidemiologic figures of AIDP in HIV disease are unknown, though there is some evidence that the pleocytosis from HIV infection is directly related to the **neuropathy**. The mainstay of treatment is plasmapheresis and IV immune globulin, and the prognosis does not appear to be different from non-HIV associated AIDP.

CIDP (Chronic inflammatory demyelin-ating polyneuropathy) may also be the presenting illness for HIV disease and generally occurs with CD4 counts between 200-500 cells/mm^3. This condition can be thought of as a chronic form of GBS. Patients typically have absent or reduced reflexes as well as patchy numbness and weakness. CSF examination often shows a mild mononuclear pleocytosis in addition to an elevated protein. Treatment centers on immunomodulation and is potentially problematic in the setting of HIV disease given the pre-existing immuno-suppression. Corticosteroids, plasmapheresis, IVIG and cyclosporin have all been used successfully. **No** clear guidelines for anti-retroviral therapy exist, though it seems prudent to avoid potentially neurotoxic agents.

Mononeuropathies such as Bell's palsy have been suggested to occur at higher rates in HIV-infected people, though precise figures are unknown. Mononeuropathy multiplex (MM) can occur early in HIV disease as a result of immune dysfunction or vasculitis. Clinically, these patients have asymmetric, patchy sensory or motor deficits. In vasculitis, pain generally precedes motor or sensory deficits. Nerve biopsy is necessary to confirm the diagnosis. Electrodiagnostic testing is helpful in confirming asymmetric abnormalities, excluding multiple entrapment neuropathies as well as in identifying an appropriate site for biopsy. Therapy is determined by etiology, with vasculitis requiring immunosuppression.

An often painful, distal sensorimotor **neuropathy** associated with CD8 hyper-lymphocytosis and a Sjögren's-like syndrome can occur during symptomatic HIV infection and potentially could be confused with HIV-associated sensory **neuropathy**. This disorder has been termed diffuse infiltrative lymphocytosis syndrome (DILS). Only patients with CD8 hyperlymphocytosis and MHC class HLA DR5 or DR6 alleles appear to be at risk, and the mean CD4 cell count in DILS patients is 260 cells/mm^3, with one third having AIDS. Clinically, DILS develops as a subacute, often painful **neuropathy** commonly accompanied by parotid enlargement and sicca syndrome. Many patients have systemic involvement, such as lymphadenopathy, splenomegaly or intersitial pneumonia. Electrodiagnostic testing generally reveals a length-dependent axonal process, though evidence of demyelination is present in 15% of cases. CSF analysis is notable for a nonspecific mononuclear pleocytosis and striking xanthochromia. Pathology reveals a non-destructive angiocentric T cell infiltrate in the epi- and endoneurium. Treatment is centered on HIV suppression, with HAART resulting in complete recovery in two-thirds of patients.

A progressive polyradiculopathy (PP) can develop in patients with advanced HIV disease and CD4 cell counts of 50 cells/mm^3 or less. Patients usually present with subacute low back and radicular pain over a period of days. Weakness progresses to flaccid paralysis with sensory loss and frequently urinary difficulties. The upper extremities are rarely involved. The most common cause is CMV, with approximately 10% of cases occurring while on CMV maintenance therapy and 38% having evidence of CMV infection elsewhere, usually retinitis. Other causes include lymphomatous meningitis, syphilitic

radiculopathy, herpes simplex or herpes zoster myeloradiculopathy, toxoplasmosis, and mycobacterial infection. CSF analysis is essential in distinguishing among these possibilities. A predominant polymorpho-nuclear pleocytosis, commonly above 200 cells/mm^3, with a low CSF glucose is typical of CMV infection. CSF cytology, VDRL and viral PCR studies are also useful, while imaging studies are important in ruling out mass lesions. Early recognition and treatment of CMV polyradiculopathy can prevent an otherwise devastating outcome.

A mononeuropathy multiplex occurring in the setting of advanced HIV disease is almost always due to CMV infection. As with CMV polyradiculopathy, evidence of CMV infection elsewhere is common, particularly in the retina. CSF analysis in CMV mono-**neuropathy** multiplex differs from CMV PP in that a polymorphonuclear pleocytosis is often not present, though CMV PCR is usually positive. Most patients improve after treatment with foscarnet or ganciclovir.

[Return to top]

The HIV Associated Sensory Neuropathies

The most common **peripheral** nerve complication in HIV infection is a length-dependent, axonal sensory **neuropathy** that is dominated by neuropathic pain. The HIV associated sensory neuropathies (HIV-SN) include both distal sensory polyneuropathy (DSP) due to IV infection, and antiretroviral drug toxic **neuropathy** (ATN) caused by the dideoxynucleosides (ddC, d4T, and ddI). These two forms of HIV-SN are pheno-typically identical and affect approximately 30% of AIDS patients. They are characterized by painful dysesthesias in the feet and legs, described as "painful numbness," "aching," or "burning." HIV-SN is a major source of morbidity among AIDS patients. Symptoms are generally worse at night and can be aggravated by innocuous stimuli, such as bed sheets or wearing shoes. Abnormalities on examination are generally limited to sensory nerve fibers and include reduced or absent ankle reflexes and increased vibratory and pin thresholds. Affected patients can often test normally on routine nerve conduction testing. This reflects the prominent small caliber sensory nerve involvement in HIV-SN and the fact that these nerves are "invisible" to nerve conduction/EMG testing. Skin biopsy and visualization of epidermal nerve fibers is a useful diagnostic tool in such instances.

DSP is associated with advanced HIV disease, with lower CD4 count and higher viral load being risk factors. An association between viral set point and the subsequent development of HIV-SN has been suggested. Autopsy studies have demonstrated pathological abnormalities in the **peripheral** nerves of virtually all patients dying from AIDS, and sub-clinical abnormalities in **peripheral** nerve function are common on detailed testing. This suggests a gradual progression of nerve damage in HIV disease with much of it being silent, before development of DSP. HIV itself appears to play an indirect role in the development of DSP in that macrophage activation and aberrant proinflammatory cytokines are thought to mediate the neurotoxicity.

While the incidence of most neurological complications of HIV has fallen dramatically over the past decade, HIV-SN has become more prevalent, coinciding with the use of dideoxynucleoside drugs. ATN has sub-sequently emerged as a common cause of HIV-SN.

The only distinguishing characteristic of ATN is the temporal association with use of dideoxynucleoside NRTIs; otherwise the two conditions are virtually indistinguishable. The onset of ATN ranges from one week to 6 months, depending on the NRTI and the dose administered. Symptoms may continue to worsen after discontinuation of the offending agent, followed by improvement in most but not all patients over a period of weeks to months. Pathophysiologically, ATN differs from DSP and has been linked to mitochondrial dysfunction. Importantly, patients with pre-existing DSP appear to be at increased risk of developing ATN. Dideoxynucleoside NRTIs may trigger neuropathic symptoms in patients with pre-exiting, silent neuronal damage due to HIV infection.

Treatment of HIV-SN is largely symptomatic. In the case of ATN, the suspected offending agent should be discontinued or the dose reduced, if possible. Several agents that have been **effective** in other painful neuropathies have not shown efficacy in HIV-SN, including amitriptyline, mexiletine, topical capsaicin and acupuncture. Both 5% lidocaine and gabapentin have been used successfully in open-label trials, but controlled data is lacking. Anecdotal evidence suggests that topiramate may also be beneficial. Currently, the only therapies shown to be **effective** in randomized, placebo-controlled clinical trials are lamotrigine and recombinant human nerve growth factor, of which the latter is not commercially available. The beneficial effect of lamotrigine appears to be most pronounced in ATN patients, and the risk of rash is minimal if the dose is slowly titrated upwards. Both lamotrigine and topiramate have the added advantage of not affecting the cytochrome P450 pathway and therefore not interacting with antiretroviral agents.

[Return to top]

Conclusions

Peripheral nerve disease is common in HIV infection. Other infectious causes are infrequent but important to recognize, as they are potentially treatable. HIV-SN is the most prevalent **neuropathy** associated with HIV infection and is now the most common neurological complication of HIV disease. Two forms of HIV-SN exist, distal sensory polyneuropathy (DSP) related to macro-phage and cytokine dysregulation resulting from HIV infection and antiretroviral toxic **neuropathy** (ATN), produced by mitochondrial dysfunction. ATN can require alteration of antiviral regimens at the risk of reducing virologic control and may act to trigger or unmask clinically silent HIV-mediated **neuropathy**.

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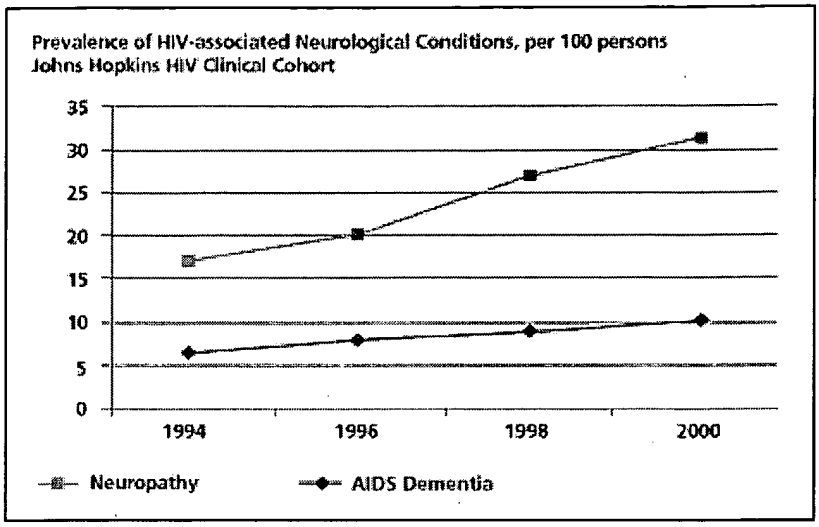

Return to top | Next Article: **Substance Abuse and HIV** | 2002 Table of Contents

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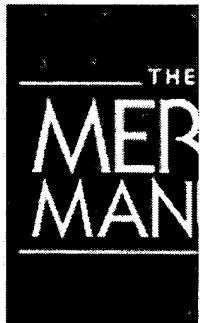
Peripheral Neuropathy

***Peripheral neuropathy** is dysfunction of a spinal nerve or nerves distal to a plexus or root. It includes numerous syndromes characterized by varying degrees of sensory disturbances, pain, muscle weakness and atrophy, diminished deep tendon reflexes, and vasomotor symptoms, alone or in any combination. Initial classification is based on history and physical examination and must be confirmed with electromyography and nerve conduction velocity studies. **Treatment** is aimed mainly at the cause.*



Peripheral neuropathy may affect a **single** nerve (mononeuropathy), ⩾ 2 discrete nerves in separate areas (multiple mononeuropathy), or many nerves simultaneously (polyneuropathy).

MONONEUROPATHIES

***Single** and multiple mononeuropathies are characterized by sensory disturbances a in the distribution of the affected nerve or nerves. Diagnosis is clinical but should be with electrodiagnostic tests. **Treatment** is directed at the cause, sometimes with spli NSAIDs, corticosteroid injections, and, for severe cases of nerve entrapment, surger*

Trauma is the most common cause of acute mononeuropathy. Violent muscular acti overextension of a joint may cause focal **neuropathy**, as may repeated small traum gripping of small tools, excessive vibration from air hammers). Prolonged, uninterrup at bony prominences can cause pressure **neuropathy**, usually affecting superficial n

radial, peroneal), particularly in thin people; such pressure may occur during sound s intoxication, bicycle riding, or anesthesia. Compression of nerves in narrow canals c entrapment **neuropathy** (eg, in carpal tunnel syndrome). Nerve compression by a tu hyperostosis, a cast, crutches, or prolonged cramped postures (eg, during gardening compression paralysis. Hemorrhage into a nerve, exposure to cold or radiation, or di invasion may cause **neuropathy**.

Multiple mononeuropathy (mononeuritis multiplex) is usually secondary to connective disorders (eg, polyarteritis nodosa, SLE, Sjögren's syndrome, RA), sarcoidosis, meta disorders (eg, diabetes, amyloidosis), or infectious disorders (eg, Lyme disease, HIV leprosy). Diabetes usually causes sensorimotor distal polyneuropathy (see **Peripher** System Disorders: Polyneuropathy).

Symptoms and Signs

Single and multiple mononeuropathies are characterized by pain, weakness, and pa the distribution of the affected nerve or nerves. Pure motor nerve involvement begins weakness; pure sensory nerve involvement begins with sensory disturbances withou Multiple mononeuropathy is often asymmetric at its onset; nerves may be involved al progressively. Extensive involvement of many nerves may simulate polyneuropathy.

Ulnar nerve palsy of the elbow is often caused by trauma to the nerve in the ulnar g elbow by repeated leaning on the elbow or by asymmetric bone growth after a childh (tardy ulnar palsy). The ulnar nerve can also be compressed at the cubital tunnel. Cc the level of the elbow can cause paresthesias and a sensory deficit in the 5th digit ar of the 4th digit; the thumb adductor, 5th digit abductor, and interosseous muscles are may be atrophied. Severe chronic ulnar palsy causes a clawhand deformity.

Carpal tunnel syndrome (see also Hand Disorders: Carpal Tunnel Syndrome) may or bilateral. It results from compression of the median nerve in the volar aspect of the between the transverse superficial carpal ligament and the flexor tendons of the fore The compression causes paresthesias in the radial-palmar aspect of the hand and p wrist and palm. Pain may also occur in the forearm and shoulder. Pain may be more night. A sensory deficit in the palmar aspect of the 1st 3 fingers may follow, and the r control thumb abduction and opposition may become weak and atrophied. Sensory s to this syndrome should be distinguished from C6 root dysfunction due to cervical ra by electromyography (EMG) if needed.

Peroneal nerve palsy is usually caused by compression of the nerve against the lat the fibular neck. It is most common among emaciated bedbound patients and thin pe habitually cross their legs. It causes footdrop (weakened dorsiflexion and eversion of and, occasionally, a sensory deficit in the anterolateral aspect of the lower leg and th the foot or in the web space between the 1st and 2nd metatarsals.

Radial nerve palsy (Saturday night palsy) is caused by compression of the nerve ag humerus, as when the arm is draped over the back of a chair for a long time (eg, dur intoxication or deep sleep). Typical symptoms include wristdrop (weakness of the wri extensors) and sensory loss in the dorsal aspect of the 1st dorsal interosseous musc

Diagnosis and Treatment

Electrodiagnostic tests are generally obtained, either to clarify diagnosis or to assess prognosis.

Underlying disorders are treated. **Treatment** of compression **neuropathy** depends c Often, fixed compression (eg, by tumor) must be relieved surgically. Symptoms of tra

compression usually resolve with rest, heat, NSAIDs, and avoidance or modification activity. Patients with carpal tunnel syndrome sometimes benefit from corticosteroid i all types, braces or splints are often used pending resolution. Surgery should be con progression occurs despite conservative treatment.

POLYNEUROPATHY

*A polyneuropathy is a diffuse **peripheral** nerve disorder not confined to the distributi nerve or a **single** limb. Electrodiagnostic tests should always be performed to classif structures involved, distribution, and severity of the disorder in order to focus the sea underlying cause. **Treatment** is directed toward attenuating or removing the underlyi*

Some polyneuropathies (eg, due to lead toxicity, dapsone use, tick bite, porphyria, o Barré syndrome) affect primarily motor fibers; others (eg, due to dorsal root ganglion leprosy, AIDS, diabetes mellitus, or chronic pyridoxine intoxication) affect primarily s Some disorders (eg, Guillain-Barré syndrome, Lyme disease, diabetes, diphtheria) c cranial nerves. Certain drugs and toxins can affect sensory or motor fibers or both (s Peripheral Nervous System Disorders: Toxic Causes of Neuropathies).

Table 5

Toxic Causes of Neuropathies

Type	Causes
Axonal motor	Gangliosides; with prolonged exposure, lead, mercury, misoprostol, tetanus, tick paralysis
Axonal sensorimotor	Acrylamide, alcohol (ethanol), allyl chloride, arsenic, cadmium, carbon disulfide, chlorphenoxy compounds, ciguatoxin, dapsone, colchicine, cyanide, DMAPN, disulfiram, ethylene oxide, lithium, methyl bromide, nitrofurantoin, organophosphates, podophyllin, polychlorinated biphenyls (PCBs), saxitoxin, Spanish toxic oil, taxol, tetrodotoxin, thallium, trichloroethylene, TOCP, vacor (PNU), vinca alkaloids
Axonal sensory	Almitrine, bortezomib, chloramphenicol, dioxin, doxorubicin, ethambutol, ethionamide, etoposide, gemcitabine, glutethimide, hydralazine, ifosfamide, interferon-α, isoniazid, lead, metronidazole, misonidazole, nitrous oxide, nucleosides (didanosine [ddI], stavudine [d4T], zalcitabine [ddC]), phenytoin, platinum analogs, propafenone, pyridoxine, statins, thalidomide
Demyelinating	Buckthorn, chloroquine, diphtheria, hexachlorophene, muzolimine, perhexiline, procainamide, tacrolimus tellurium, zimeldine
Mixed	Amiodarone, ethylene glycol, gold, hexacarbons, n-hexane, Na cyanate, suramin

DMAPN = dimethylaminopropionitrile; TOCP = triorthocresyl phosphate; PNU = N-3 pyrid nitrophenyl urea.

Symptoms and Signs

Because pathophysiology and symptoms are related, polyneuropathies are often cla area of dysfunction: myelin, vasa nervorum, or axon. Hereditary neuropathies are dis below.

Myelin dysfunction: Myelin dysfunction polyneuropathies most often result from a p immune response triggered by an encapsulated bacterium (eg, *Campylobacter* sp), v

enteric or influenza viruses, HIV), or vaccine (eg, influenza vaccine). Presumably, an these agents cross-react with antigens in the **peripheral** nervous system, causing a response (cellular, humoral, or both) that culminates in varying degrees of myelin dy acute cases (eg, in Guillain-Barré syndrome—see **Peripheral** Nervous System Diso Guillain-Barré Syndrome (GBS)), rapidly progressive weakness and respiratory failu develop.

Myelin dysfunction usually results in large-fiber sensory disturbances (paresthesias), muscle weakness greater than expected for degree of atrophy, and significantly dimi reflexes. Trunk musculature and cranial nerves may be involved. Abnormalities typic along the entire length of a nerve, producing proximal and distal symptoms. There m side asymmetries, and more rostral parts of the body may be affected before distal e Muscle bulk and tone are relatively preserved.

Vasa nervorum compromise: Chronic arteriosclerotic ischemia, vasculitis, and hyp states can compromise the vascular supply to the nerves.

Usually, small-fiber sensory and motor dysfunction occurs first. Patients typically hav often burning sensory disturbances. Abnormalities tend to be asymmetric early in the rarely affect the proximal $\frac{1}{3}$ of the limb or trunk muscles. Cranial nerve involvement in diabetes, which commonly affects the 3rd cranial (oculomotor) nerve. Later, sympt signs may appear symmetric if nerve lesions coalesce. Dysautonomia and skin chan atrophic, shiny skin) sometimes occur. Muscle weakness tends to be proportional to reflexes are rarely lost completely.

Axonopathy: Axonopathies tend to be distal; they may be symmetric or asymmetric

Symmetric axonopathies result most often from toxic-metabolic disorders. Common include diabetes mellitus, chronic renal insufficiency, and adverse effects of chemoth (eg, vinca alkaloids). Axonopathy may result from nutritional deficiencies (most comr vitamin B) or from excess intake of vitamin B_6 or alcohol. Less common metabolic ca hypothyroidism, porphyria, sarcoidosis, and amyloidosis. Other causes include certai (eg, Lyme disease), drugs (eg, nitrous oxide), and exposure to certain chemicals (eg Orange, n-hexane) or heavy metals (eg, lead, arsenic, mercury). In a paraneoplastic associated with small-cell lung cancer, loss of dorsal root ganglia and their sensory a in subacute sensory **neuropathy**.

Primary axon dysfunction may begin with symptoms of large- or small-fiber dysfuncti Usually, the resulting **neuropathy** has a distal symmetric, stocking-glove distribution affects the lower extremities before the upper extremities and progresses symmetric distal to proximal areas.

Asymmetric axonopathy can result from parainfectious or vascular disorders.

Diagnosis

Clinical findings, particularly tempo of onset, aid in diagnosis and identification of the Asymmetric neuropathies suggest a disorder affecting the myelin sheath or vasa ner Symmetric, distal neuropathies suggest toxic or metabolic causes. Slowly progressiv neuropathies tend to be inherited or due to long-term toxic exposure or metabolic dis neuropathies suggest an autoimmune response, vasculitis, or a postinfectious cause ulcers, and Raynaud's phenomenon in patients with an asymmetric axonal **neuropat** hypercoagulable state or parainfectious or autoimmune vasculitis. Weight loss, fever lymphadenopathy, and mass lesions may suggest a tumor or paraneoplastic syndror

Electrodiagnostic tests: Regardless of clinical findings, electromyography (EMG) a conduction velocity studies are necessary to classify type of **neuropathy**. At a minir both lower extremities should be done to assess for asymmetry and full extent of axc Because EMG and nerve conduction studies assess primarily large myelinated fiber segments, EMG may be normal in patients with proximal myelin dysfunction (eg, ear Barré syndrome) and in patients with primarily small-fiber dysfunction. In such cases sensory or autonomic testing or both may be done depending on the presenting sym

Laboratory tests: Baseline laboratory tests for all patients include CBC, electrolytes function tests, rapid plasma reagin test, and measurement of fasting blood sugar, he A_{1C}, vitamin B_{12}, folate, and thyroid-stimulating hormone. Some clinicians include se electrophoresis. The need for other tests is determined by polyneuropathy subtype.

The approach to patients with acute myelin dysfunction neuropathies is the same as with Guillain-Barré syndrome (see **Peripheral** Nervous System Disorders: Guillain-B Syndrome (GBS)); forced vital capacity is measured to check for incipient respiratory acute or chronic myelin dysfunction, tests for infectious disorders and immune dysfu including tests for hepatitis and HIV and serum protein electrophoresis, are done. In myelin-associated glycoprotein (MAG) antibodies are measured if motor dysfunction predominates; anti-sulfatide antibodies are measured if primary sensory dysfunction lumbar puncture should also be done; myelin dysfunction due to an autoimmune res causes albuminocytologic dissociation: increased CSF protein (> 45 mg%) but norm ($\leqslant$ 5/μL).

For asymmetric axonal polyneuropathies, tests for hypercoagulable states and paran autoimmune vasculitis, particularly if suggested by clinical findings, should be done; is ESR, serum protein electrophoresis, and measurement of rheumatoid factor, antin antibodies, and serum CPK. CPK may be elevated when rapid onset of disease resu infarction. Coagulation studies (eg, protein C, protein S, antithrombin III, anticardiolip homocysteine levels) should be done only if suggested by personal or family history. sarcoidosis, hepatitis C, or Wegener's granulomatosis should be done only if sugges symptoms and signs. If **no** cause is identified, nerve and muscle biopsy should be d affected sural nerve is usually biopsied. A muscle adjacent to the biopsied sural nerv quadriceps, biceps brachii, or deltoid muscle may be biopsied. The muscle should b moderate weakness that has not been tested by needle EMG. Yield is higher if the c muscle has EMG abnormalities. Nerve biopsies tend to be more useful in asymmetri axonopathies than in other polyneuropathy subtypes.

If initial tests do not identify the cause of distal symmetric axonopathies, a 24-h urine tested for heavy metals, and urine protein electrophoresis is done. If chronic heavy n poisoning is suspected, testing of hairs from the pubis or axillary region may help. Hi physical examination should determine whether tests for other causes are needed.

Treatment

Treatment focuses on correcting the causes when possible (see elsewhere in the m causative drug or toxin can be eliminated, or a dietary deficiency corrected. Althoug actions may halt progression and lessen symptoms, recovery is slow and may be inc the cause cannot be corrected, **treatment** focuses on minimizing disability and pain. occupational therapists can recommend useful assistive devices. Amitriptyline, g mexiletine, and topical lidocaine may relieve neuropathic pain (eg, diabetic burn

For myelin dysfunction polyneuropathies, immune system–modifying treatments are plasmapheresis or IV immune globulin for acute myelin dysfunction and corticosteroi antimetabolite drugs for chronic myelin dysfunction.

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Back to Top

Previous: Nerve Root Disorders

Next: Plexu

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REVIEW

Neuropathic pain: a practical guide for the clinician

Ian Gilron, C. Peter N. Watson, Catherine M. Cahill, Dwight E. Moulin

ABSTRACT

Neuropathic pain, caused by various central and peripheral nerve disorders, is especially problematic because of its severity, chronicity and resistance to simple analgesics. The condition affects 2%–3% of the population, is costly to the health care system and is personally devastating to the people who experience it. The diagnosis of neuropathic pain is based primarily on history (e.g., underlying disorder and distinct pain qualities) and the findings on physical examination (e.g., pattern of sensory disturbance); however, several tests may sometimes be helpful. Important pathophysiologic mechanisms include sodium- and calcium-channel upregulation, spinal hyperexcitability, descending facilitation and aberrant sympathetic–somatic nervous system interactions. Treatments are generally palliative and include conservative nonpharmacologic therapies, drugs and more invasive interventions (e.g., spinal cord stimulation). Individualizing treatment requires consideration of the functional impact of the neuropathic pain (e.g., depression, disability) as well as ongoing evaluation, patient education, reassurance and specialty referral. We propose a primary care algorithm for treatments with the most favourable risk–benefit profile, including topical lidocaine, gabapentin, pregabalin, tricyclic antidepressants, mixed serotonin–norepinephrine reuptake inhibitors, tramadol and opioids. The field of neuropathic pain research and treatment is in the early stages of development, with many unmet goals. In coming years, several advances are expected in the basic and clinical sciences of neuropathic pain, which will provide new and improved therapies for patients who continue to experience this disabling condition.

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Neuropathic pain, caused by a lesion of the nervous system,[1,2] is especially problematic because (a) it is often experienced in parts of the body that otherwise appear normal, (b) it is generally chronic, severe[3] and resistant to over-the-counter analgesics,[4] and (c) it is further aggravated by allodynia (touch-evoked pain).[5] It may result from various causes that affect the brain, spinal cord and peripheral nerves, including cervical or lumbar radiculopathy, diabetic neuropathy, cancer-related neuropathic pain, postherpetic neuralgia, HIV-related neuropathy, spinal cord injury, trigeminal neuralgia and complex regional pain syndrome type II, among others.[6] Complex regional pain syndrome type I is not considered a cause, because there is no definable nerve lesion. The epidemiology of neuropathic pain has not been adequately studied, partly because of the diversity of the associated conditions. Current pooled estimates suggest that neuropathic pain may affect as much as 3% of the population.[7–13]

The personal impact of neuropathic pain is most vividly appreciated by people who experience this devastating condition. Those affected have described their pain using the McGill Pain Questionnaire[14] with descriptors such as "punishing–cruel" and "tiring–exhausting."[15,16] Ample evidence indicates that neuropathic pain impairs patients' mood, quality of life, activities of daily living and performance at work.[9,17,18] People with the condition have been found to generate 3-fold higher health care costs compared with matched controls.[19] In the United States, health care, disability and related costs associated with chronic pain have been estimated at $150 billion annually,[20] of which almost $40 billion is attributable to neuropathic pain.

Clinical presentation and patient evaluation

The blockade of nerve conduction in neuropathic conditions causes nerve dysfunction, which can result in numbness, weakness and loss of deep tendon reflexes in the affected nerve area. Neuropathic conditions also cause aberrant symptoms of spontaneous and stimulus-evoked pain. Spontaneous pain (continuous or intermittent) is commonly described as burning, shooting or shock-like.[15,21–26] Stimulus-evoked pain includes allodynia (pain evoked by a nonpainful touch) and hyperalgesia (increased pain evoked by a painful stimulus). Allodynia can be caused by the lightest stimulation, such as skin contact with clothing or a light breeze. These sensory abnormalities may extend beyond nerve distributions (Fig. 1), which may lead to the inappropriate diagnosis of a functional or psychosomatic disorder. The diagnosis of neuropathic pain is based primarily on history and findings on physical examination.[27]

Assessment of the patient with suspected neuropathic pain should focus on ruling out treatable conditions (e.g., spinal cord compression, neoplasm), confirming the diagnosis of neuropathic pain and identifying clinical features (e.g., insomnia, autonomic neuropathy) that might help individualize treatment. Box 1 lists principal details of the clinical evaluation, including history, physical examination and special tests.

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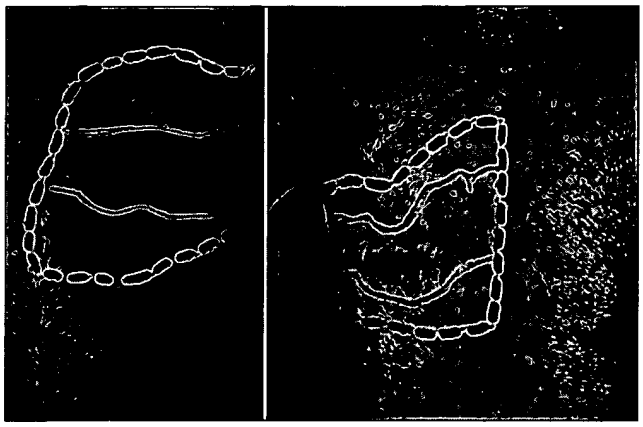

Fig. 1: Man with postherpetic neuralgia in the left fifth and sixth thoracic dermatomes. Red lines delineate area of sensory loss, and black dashed lines delineate area of allodynia (touch-evoked pain). Extension of allodynia above and below the originally affected dermatomes is a feature of central sensitization.

Pathophysiology and molecular mechanisms of neuropathic pain

Table 1 highlights the clinical and pathophysiologic features of common neuropathic pain syndromes that are caused by nerve injury or dysfunction. Knowledge of the cellular and molecular mechanisms of neuropathic pain has advanced with the development of various experimental models of nerve injury.[50] Both peripheral and central mechanisms (Fig. 2) have been proposed as being relevant to the pathogenesis of neuropathic pain.[51]

Peripheral mechanisms

Regeneration after nerve injury results in the formation of neuromas[52,53] and sprouting of new nerve projections among uninjured neighbouring neurons.[54] Collateral sprouting then leads to altered sensory properties that may be realized as expanded receptive fields. Uncontrolled neuronal firing after experimental nerve injury is largely attributed to increased expression of sodium channels. This mechanism is supported by several lines of evidence, including blockade of neuropathic pain with sodium-channel–blocking local anesthetics.[55] Demyelination of diseased nerves may be another cause of increased neuronal excitability.[56]

In addition to sodium channels, expression of voltage-gated calcium channels is also increased following nerve injury.[57] Calcium entry through voltage-gated calcium channels is necessary for the release of substance P[58] as well as glutamate from injured peripheral nerves. Within the dorsal root ganglion, increased expression of the α-2-delta subunit of voltage-gated calcium channels correlates with onset and duration of allodynia.[59] Clinical support of the role of this protein in neuropathic pain arises from the analgesic efficacy of α-2-delta voltage-gated calcium-channel antagonists, gabapentin and pregabalin.[60,61]

Central mechanisms

Sustained painful stimuli result in spinal sensitization,[62] which is defined as heightened sensitivity of spinal neurons, reduced activation thresholds and enhanced responsiveness to synaptic inputs (i.e., more likely to transmit pain to the brain).[63] This can manifest in expansion of the affected area, increased response to painful inputs and transmission of pain following nonpainful stimuli.[64] Central sensitization is largely mediated by the *N*-methyl-D-aspartate (NMDA) receptor. Although experimental NMDA-receptor blockade clearly suppresses central sensitization,[65] analgesic efficacy of NMDA antagonists has been disappointing, likely because of the narrow therapeutic window of available agents.[61]

Activation of descending pathways (the periaqueductal grey-rostral ventromedial medulla)[66] has been shown to reduce pain transmission in animals[67] and humans[68] and is thought to contribute to the analgesic effect of opioids and antidepressants. Paradoxically, this system can also facilitate pain transmission[69] and may contribute to some chronic pain states.[70]

Sympathetically maintained pain

The importance of the sympathetic nervous system in neuropathic pain has been demonstrated by analgesia following sympathectomy in animals[71] and humans,[72] and by pain exacerbation through activation of the sympathetic nervous system.[73] Sympathetically maintained pain may be explained by sprouting of sympathetic neurons into dorsal root ganglia of injured sensory neurons[74] and postinjury sprouting of sympathetic fibres into the dermis.[75]

Current management

Nonpharmacologic

Although many patients with neuropathic pain pursue complementary and alternative treatments, rigorous evidence supporting efficacy of nondrug therapy is limited. Some reports suggest benefits of conservative interventions such as exercise,[76] transcutaneous electrical nerve stimulation,[77] percutaneous electrical nerve stimulation,[78] graded motor imagery[79] and cognitive behavioural therapy or supportive psychotherapy.[80]

Pharmacologic

One approach to estimate treatment efficacy using randomized controlled trial (RCT) data is based on the number-needed-to-treat (NNT) to obtain at least 50% pain relief in one patient. The NNT concept is hampered by methodologic variability across different RCTs, the short-term nature of most RCTs and the lack of consideration for other important outcomes (e.g., disability, quality of life). Also, most RCTs have involved patients with diabetic peripheral neuropathy and postherpetic neuralgia, and the results do not necessarily apply to all neuropathic pain conditions.

Antidepressants

Tricyclic antidepressants have repeatedly been shown to reduce neuropathic pain.[81] Analgesic actions may be attributable to noradrenaline and serotonin reuptake blockade (presumably enhancing descending inhibition), NMDA-receptor antagonism and sodium-channel blockade.[82] The NNT is about 3 both for balanced noradrenaline and serotonin reuptake inhibitors (e.g., amitriptyline) and predominantly noradrenaline reuptake inhibitors (e.g., nortriptyline).[61]

Selective serotonin reuptake inhibitors (NNT = 6.7)[83] and mixed serotonin–noradrenaline reuptake inhibitors (venlafaxine and duloxetine,[84] NNT = 4.1–5.5)[61] do not appear to be as effective as tricyclic antidepressants.

Anticonvulsants

Based on methodologically flawed trials, carbamazepine and phenytoin have NNTs of 2.1–2.3 for diabetic peripheral neuropathy.[61] Both have significant adverse effects, making them generally poor candidates for first-line therapy. Carbamazepine, however, is still considered first-line therapy for trigeminal neuralgia, a unique neuropathic pain condition (NNT = 1.7).[61] Oxcarbazepine, a newer anticonvulsant structurally related to carbamazepine, may also be useful; however, only one RCT (in diabetic peripheral neuropathy) has been published.[85]

Gabapentin, an α-2-delta subunit voltage-gated calcium-channel antagonist,[86] has repeatedly demonstrated analgesic

Box 1: Clinical evaluation of patients with suspected neuropathic pain

History

Pain intensity

- 0-10 rating scale (0 = no pain, 10 = worst pain imaginable)
- Rate pain at initial presentation and at subsequent visits to track treatment response

Sensory descriptors[15,21-26]

- Pain qualities: hot, burning, sharp, stabbing, cold, allodynia (pain brought on by light touch, clothing or bed sheets)
- Common nonpainful sensations: tingling, prickling, itching, numbness and "pins and needles"

Temporal variation

- Neuropathic pain often gets worse towards the end of the day[28]
- Neoplastic process should be suspected if pain has been progressively increasing over recent months

Functional impact

- Effect of pain on sleep,[29] ambulation, self-care, activities of daily living, work, social or sexual function, mood[30] and suicidal ideation[31]

Attempted treatments

- Neuropathic pain is generally resistant to acetaminophen and NSAIDs
- Determine and document adequacy of dose titration for titratable drugs (e.g., dose reached and duration of treatment, drug treatment stopped owing to adverse effects or lack of efficacy)[32]

Alcohol or substance abuse

- Addiction history will affect decision to prescribe opioids or cannabinoids
- Consider earlier involvement with a psychologist or psychiatrist[33]
- Consider safety of sedative analgesics with alcohol or other sedatives

Physical examination

Gross motor examination

- Motor weakness may occur around the involved nerves
- Attempt to differentiate between true weakness and antalgic weakness

Deep tendon reflexes

- May be diminished or absent around the involved nerves

Sensory examination

- Light touch, pin prick, vibration sense and proprioception may be diminished or absent in the involved nerve territory
- Sensory disturbance may aberrantly extend beyond a discrete nerve territory
- Dynamic allodynia (pain due to cotton wool lightly moving across the skin)
- Thermal allodynia (burning sensation in response to ice cube on skin)
- Pinprick hyperalgesia (exaggerated pain following pinprick to the skin)
- Pain when straight leg is raised, suggestive of irritation of lumbar nerve root
- Elicitation of myofascial trigger points to favour a diagnosis of myofascial pain over neuropathic pain
- Possible presence of Tinel's sign (distally radiating paresthesias upon percussion of damaged or regenerating nerve fibres)

Skin examination

- Alterations in temperature, colour, sweating and hair growth suggestive of complex regional pain syndrome[34]
- Residual dermatomal scars consistent with previous herpes zoster (shingles) infection
- Characteristic skin changes consistent with diabetes mellitus

Special tests

CT and MRI scans

- Facilitate specific diagnosis (e.g., herniated disc, nerve infiltration by tumour)

Electromyography and nerve conduction studies

- May provide objective evidence of nerve injury or dysfunction[35]
- Nerve conduction studies evaluate large fibre function; therefore, small fibre neuropathy cannot be ruled out if results of nerve conduction studies are normal

Three-phase nuclear medicine bone scan

- May help diagnose complex regional pain syndrome [36]

Clinical biochemistry

- Conduct tests to help identify cause of neuropathy; for example, glucose tolerance testing, thyroid function, measurement of vitamin B_{12} levels, CD4+ T-lymphocyte count

efficacy and improvements in mood and sleep in several RCTs (NNT = 3.8).[60,61] Pregabalin is a gabapentin analogue with a similar mechanism, higher calcium-channel affinity and better bioavailability.[60,87] Pregabalin was superior to placebo in several RCTs in diabetic peripheral neuropathy and postherpetic neuralgia (NNT = 4.2).[61]

RCTs of other anticonvulsants, including valproate, lamotrigine and topiramate, have had equivocal results.[61]

Opioid analgesics

The role of opioid analgesics in neuropathic pain has been controversial. However, a recent meta-analysis provides convincing evidence of benefit.[88] Although 14 short-term RCTs (< 24 hours) showed contradictory results, 8 intermediate-term RCTs (≤ 8 weeks) demonstrated important efficacy. These RCTs demonstrated, on average, a 20%–30% pain reduction. For morphine and oxycodone, the NNT ranged from 2.5 to 2.6.[61] However, beneficial effects on mood, quality of life and disability are not consistent.[89,90] There were no reports of addiction or abuse in these RCTs, although the risk is likely to be low given the common exclusion criterion of substance abuse history.[88] Currently, there is a dearth of evidence supporting the long-term efficacy of opioids in controlling neuropathic pain. However, the results of a recent retrospective review involving more than 100 patients (most of whom had neuropathic pain) who had received chronic opioid therapy for 1 year or more suggest that many patients may continue to enjoy persistent pain relief with opioids.[91]

Tramadol is a weak opioid and a mixed serotonin–noradrenaline reuptake inhibitor.[92] Three RCTs of tramadol for neuropathic pain have yielded an overall NNT of 3.9.[61]

Methadone is a synthetic opioid potentially useful for controlling neuropathic pain because of its NMDA-antagonist properties.[93] However, its long half-life (24–36 hours) necessitates extremely careful dose titration.[94] Two small RCTs of methadone demonstrated benefit in managing neuropathic pain,[95,96] and open-label experience suggests promise in a wide variety of neuropathic pain conditions.[97]

NMDA antagonists

Because of the critical role of NMDA activity in central sensitization,[98] NMDA antagonists hold promise in the management of neuropathic pain. Unfortunately, available agents have limited efficacy and produce intolerable side effects. Ketamine, an intravenous anesthetic with NMDA-antagonist activity, has been found to be effective in small RCTs; however,

Table 1: Clinical features and pathophysiology of common neuropathic pain syndromes

Diagnosis (inciting cause)	Typical clinical features	Putative pathophysiology and clinical pathogenesis
Painful diabetic neuropathy (hyperglycemia)	Symmetrical sensory loss and burning pain in lower legs[37]	Hyperglycemia, hyperlipidemia, hypoinsulinemia, growth factor deficiency → oxidative stress and autoimmunity → progressive demyelination and axonal loss → sensory loss, paresthesia, dysesthesias, pain and allodynia[38-40]
Lumbosacral radiculopathy (herniated intervertebral disc)	Lancinating pain radiating into the anterior thigh (L2/3) or lower leg (L4-S1) with motor weakness or sensory loss	• Spinal nerve root compression[41] • Inflammatory effects of extruded nucleus puloposus?[42] • Sensory and motor abnormalities, radiating pain
Postherpetic neuralgia (varicella zoster virus infection)	Unilateral pain, sensory loss or allodynia in the dermatome where herpes zoster had previously erupted[43]	• Dorsal horn atrophy, sensory ganglion (primary afferent neuron) cell; axon and myelin loss and fibrosis[44] • Sensitization of unmyelinated cutaneous nociceptors ("irritable nociceptors") and/or • Small fibre deafferentation and allodynia and/or • Small and large fiber deafferentation • Sensory loss, pain and allodynia[5]
HIV-related neuropathy (HIV infection)	Symmetrical painful paraesthesias, most prominent in the toes and soles of the feet[45]	• Direct viral invasion of sensory neurons? • HIV-mediated macrophage infiltration of peripheral nerves? • Neurotoxicity of reverse transcriptase inhibitors • Sensory loss, pain and allodynia[11]
Complex regional pain syndrome • Type 1 (previously "reflex sympathetic dystrophy" – no definable nerve lesion) • Type 2 (previously "causalgia" – nerve injury)	Regional (e.g., limb) pain together with edema, cutaneous blood flow and sweating abnormalities[46]	• "Coupling" of sympathetic neurons with injured sensory neurons at peripheral neuroma sites or dorsal root ganglion sites of injured afferent nerves → development of noradrenergic sensitivity following nerve injury • Pain, allodynia, hyperalgesia, edema, cutaneous blood flow and sweating abnormalities[47]
Postsurgical neuropathic pain (surgical procedure)	Peri-incisional sensory loss, pain and allodynia for more than 3 months after surgery; phantom pain following amputation or mastectomy	• Phantom pain in 30%-81% of amputations[48] • Thoracotomy pain in 11%-57%[48] • Postherniorrhaphy in 37% or less[48] • Postmastectomy pain in 66%-83%[48] • Poststernotomy in 54% or less[49]

psychomimetic side effects are dose limiting.[99] Dextromethorphan, a common cough suppressant and NMDA antagonist, has produced uncertain results in controlling neuropathic pain, showing modest benefit in diabetic peripheral neuropathy, but not in postherpetic neuralgia.[100]

Topical agents

Locally acting analgesics are attractive because they may cause minimal systemic side effects. The lidocaine patch 5% has been shown to relieve localized pain in postherpetic neuralgia with no increase in side effects (NNT = 4.4).[61] Although the lidocaine patch 5% is not available in Canada, pharmacists can make up the gel or cream at a concentration of 5%–10%.[101] Capsaicin, an ingredient of hot peppers, has shown mixed results in RCTs,[61] and some patients with postherpetic neuralgia have reported pain exacerbation. One RCT evaluating topical doxepin, capsaicin and their combination demonstrated significant analgesia with all 3 of these interventions.[102]

Miscellaneous drugs

Mexiletine, an oral antiarrhythmic agent and sodium-channel blocker, was superior to placebo in only 2 of 7 RCTs.[61] Clonidine, an α-2-agonist sympathetic blocker, was shown to be effective in a subset of patients with diabetic peripheral neuropathy.[103] Cannabinoids have been found to play a role in ex-

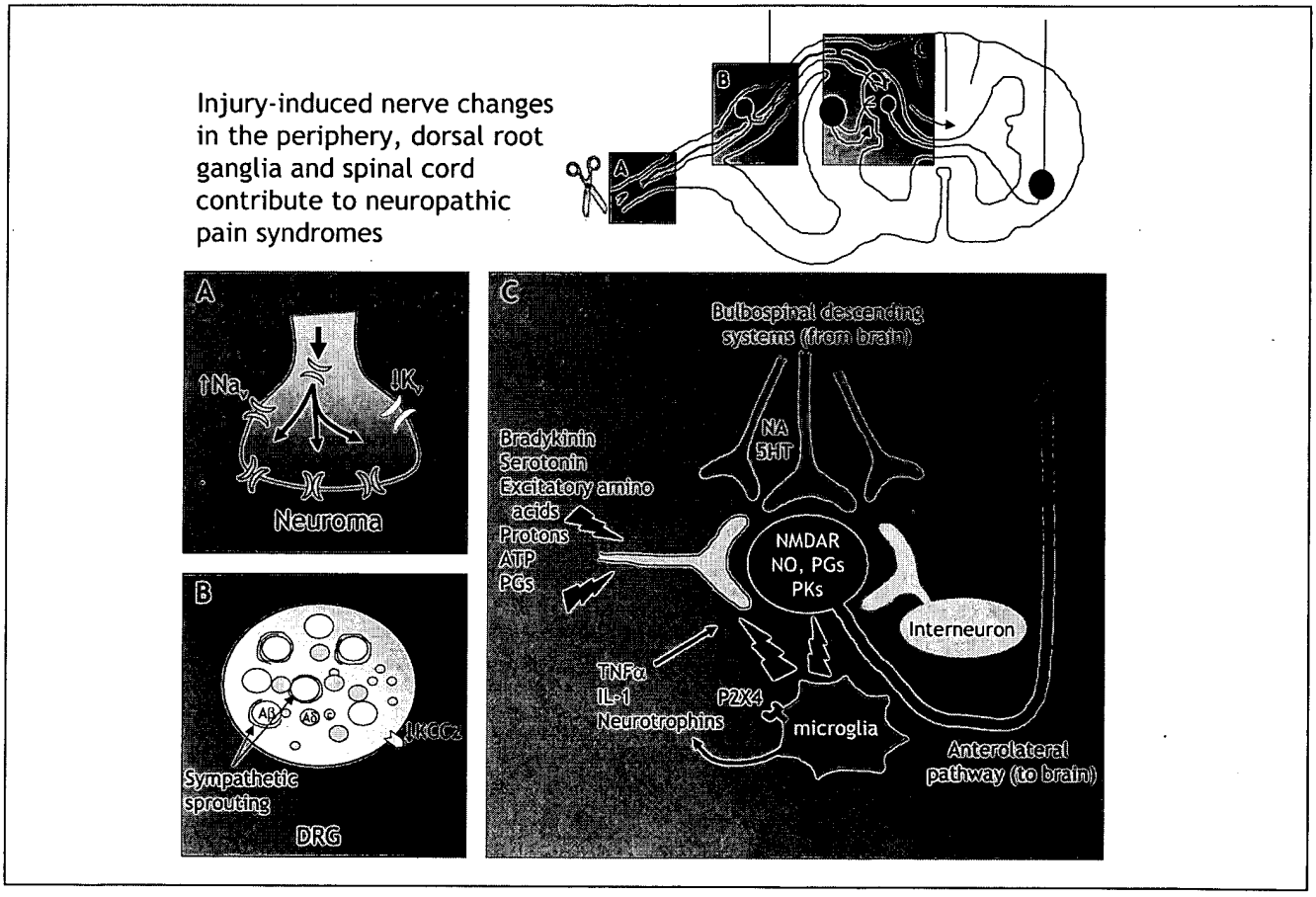

Fig 2: Neuropathic pain arises following nerve injury or dysfunction. **A:** After nerve damage, transcription and axonal trafficking of sodium channels to the site of injury is increased, with concomitant attenuation of potassium channels. The altered expression of ion channels results in neurons becoming hyperexcitable and generating ectopic activity, which is thought to lead to the genesis of spontaneous and paroxysmal pain. **B:** At the cell body of primary afferent neurons within the dorsal root ganglia (DRG), sympathetic neuronal sprouting occurs and may account for sympathetically maintained pain. **C:** Peripheral nerve injury causes a multitude of changes in gene transcription and activation of various kinases and proteins, including enhanced *N*-methyl-D-aspartate (NMDA) receptor activity. However, nerve injury also elicits hypertrophy and activation of glial cells, including microglia within the grey matter of the spinal cord. Microglia express P2X4 purinergic receptors, allowing them to be activated by adenosine triphosphate (ATP). Following activation, microglia release various pronociceptive cytokines, such as interleukin-1 (IL-1), tumour necrosis factor alpha (TNF-α) and neurotrophins, including brain-derived neurotrophic factor, which in turn exacerbates nociceptive transmission and contributes to the sensitization and maintenance of neuropathic pain. Note: Aβ = A beta neuron, Aδ = A delta neuron, C = C nociceptor, 5HT = serotonin, KCC2 = chloride transporter, NA = noradrenaline, Na_v = sodium channel, NO = nitric oxide, K_v = potassium channel, PGs = prostaglandins, PKs = protein kinases, P2X4 = purinergic receptor.

perimental pain modulation,[105] and there is growing evidence of their efficacy in managing neuropathic pain. The cannabinoid dronabinol provided modest analgesic benefit in an RCT of central pain in multiple sclerosis.[106] An oromucosal spray containing a mixture of tetrahydrocannabinol and cannabidiol provided modest benefit in another RCT of central pain in multiple sclerosis[107] and in an RCT of neuropathic pain following brachial plexus avulsion.[108]

Comparative trials

Given the limitations of comparing treatments across trials using NNTs, several investigators have compared treatments within single trials. For example, 3 comparative RCTs suggest that analgesia with desipramine[109,110] or nortriptyline[111] is comparable to that of amitriptyline but with fewer side effects. Other studies suggest that opioids may be more efficacious than tricyclic antidepressants [112] or gabapentin[16] and that gabapentin is comparable to amitriptyline[113] and venlafaxine analgesia is comparable to that of imipramine.[114] These are, however, early impressions from small RCTs. Larger RCTs that incorporate head-to-head comparisons are needed.

Combination pharmacotherapy

Given the limited effectiveness of current treatments, combining different drugs may result in improved results at lower doses and with fewer side effects. Many patients with neuropathic pain currently receive drug combinations,[115] albeit in the absence of supportive evidence. In a recent RCT, analgesia with a morphine–gabapentin combination was superior to treatment with either drug alone.[16] In a study involving 11 patients who did not respond to gabapentin, a gabapentin–venlafaxine combination was superior to gabapentin alone.[116] In another RCT, the addition of the neuroleptic fluphenazine to amitriptyline therapy provided no benefit.[117] Future trials are needed to evaluate optimal drug combinations and dose ratios as well as safety, compliance and cost-effectiveness.[118]

Trigeminal neuralgia and other paroxysmal pain

Trigeminal neuralgia and glossopharyngeal neuralgia (idiopathic or related to multiple sclerosis) are unique conditions. They are characterized by orofacial, paroxysmal, shock-like pains triggered by light, localized, tactile stimulation with minimal constant pain between paroxysms. These syndromes are also distinguished by their high responsiveness to carbamazepine.[119] Baclofen is a muscle relaxant shown to be useful in trigeminal neuralgia in the setting of resistance to carbamazepine.[104] High success rates have also been reported following invasive treatments such as microvascular decompression, trigeminal ganglion balloon compression and stereotactic (gamma knife) radiosurgery.[120]

Interventional pain management

Although rigorous supportive evidence is limited, more invasive treatments may be considered for patients with intractable neuropathic pain.[121,122] Procedures include epidural or perineural injections of local anesthetics or corticosteroids, implantation of epidural and intrathecal drug delivery systems, neural ablative procedures (e.g., Gasserion ganglion glycerol injection or gamma knife surgery) and insertion of spinal cord stimulators, just to name a few. Consideration of highly invasive procedures such as insertion of intrathecal infusion pumps or spinal cord stimulators is generally reserved for patients with no surgically treatable pathology who have failed more conservative treatments and undergone psychological evaluation.[123] Although this level of caution may also be applied to nerve block procedures, some conditions could warrant nerve blocks earlier in the clinical course. For example, sympathetic nerve blocks in early complex regional pain syndrome may be a crucial adjunct for the facilitation of physiotherapy and rehabilitation.[124]

Approach to neuropathic pain management in primary care

No single drug works for all neuropathic pain states, and given the diversity of pain mechanisms, patient responses and diseases, treatment must be individualized. Other than analgesia, factors to consider when individualizing therapy include tolerability, other benefits (e.g., improved sleep, mood and quality of life), low likelihood of serious adverse events and cost-effectiveness to the patient and the health care system.[61] The evidence-based approach presented here may require revision as newer treatments and clinical evidence become available.

Pain management requires ongoing evaluation, patient education and reassurance. Diagnostic evaluation of treatable underlying conditions (e.g., spinal cord compression, herniated disc, neoplasm) should continue concurrently with pain management. Patients require education regarding the natural history of their condition and realistic treatment expectations (e.g., current treatments are not curative and analgesia is rarely complete). Even a 30% pain reduction is clinically important to patients.[125] Pain severity, patient complexity (e.g., coexisting depression or substance abuse), failure of attempted treatments and availability of health care resources should be considered when planning referrals to pain clinics and related specialists. Patient compliance and adequacy of analgesic drug titrations (e.g., dose and duration of treatment) should be continually evaluated and documented.

Neuropathic pain is best managed with a multidisciplinary approach. Nevertheless, several different treatments can be initiated in the primary care setting (Fig. 3). Treatments with the lowest risk of adverse effects should be tried first. Evidence supporting conservative nonpharmacologic treatments (e.g., physiotherapy, exercise, transcutaneous electrical nerve stimulation) is limited; however, given their presumed safety, nonpharmacologic treatments should be considered whenever appropriate.[61] Simple analgesics (e.g., acetaminophen, NSAIDs) are usually ineffective in pure neuropathic pain but may help with a coexisting nociceptive condition (e.g., sciatica with musculoskeletal low-back pain). Early referrals to a

pain clinic for nerve blocks may be warranted in some cases to facilitate physiotherapy and pain rehabilitation.

Topical treatment with lidocaine, indicated for postherpetic neuralgia and focal neuropathy, could be tried first if it is available at a cost reasonable to the patient. For other neuropathic pain diagnoses or lidocaine treatment failures, we recommend initiating oral monotherapy with gabapentin or pregabalin, a tricyclic antidepressant, or a mixed serotonin–noradrenaline reuptake inhibitor. Of these treatments, gabapentin or pregabalin appear to be the best tolerated, with very few drug interactions. Tricyclic antidepressants appear to be more efficacious and much less expensive but have a higher likelihood of adverse effects and are relatively contraindicated for use in patients with serious cardiovascular disease (a screening electrocardiogram is recommended before prescribing tricyclic antidepressants), postural hypotension, urinary retention and angle-closure glaucoma. Among available tricyclic antidepressants, nortriptyline and desipramine are more highly recommended because of fewer side effects. Newer mixed serotonin–noradrenaline reuptake inhibitors (e.g., venlafaxine, duloxetine) may not be as efficacious as tricyclic antidepressants but appear to be better tolerated.

Little is known about whether the response to one drug predicts the response to another. However, if the first oral medication tried is ineffective or not tolerated, one might switch to alternate monotherapy. In the event that all of the first-line oral monotherapies tried are ineffective or poorly tolerated, we would then recommend initiating monotherapy with tramadol or an opioid analgesic. Long-term prescribing of opioid analgesics requires special prescribing and regulatory considerations.[126–129] In Canada, where tramadol is available only as a fixed-dose combination with acetaminophen, the upper dose limit of tramadol will be dic-

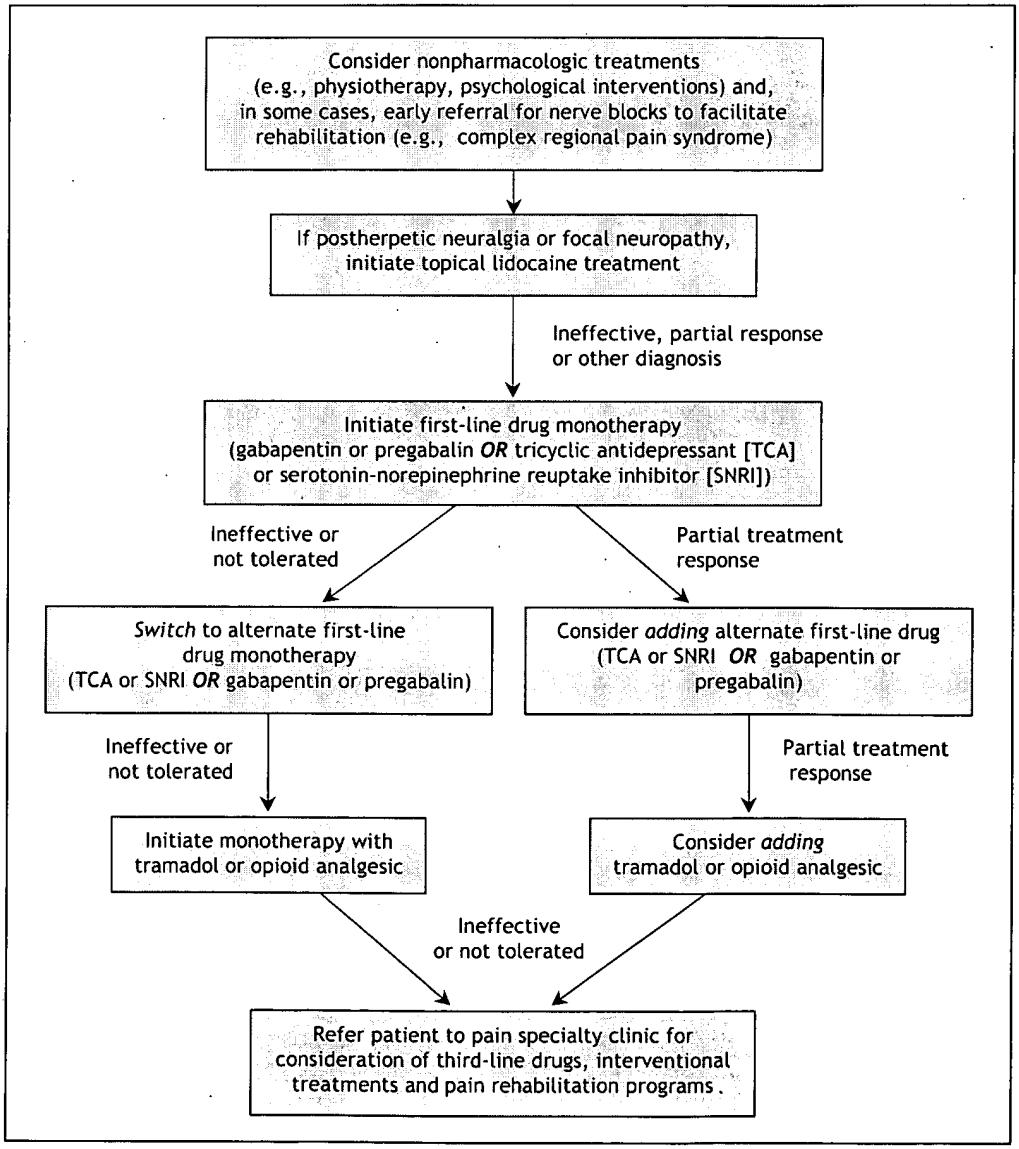

Fig. 3: Algorithm for the management of neuropathic pain in primary care.

Table 2: Neuropathic pain medications*

Drug	Drug interactions	Adverse effects	Dosage	Usual effective dose (and maximum)	Comments
Topical lidocaine 5%	Possible systemic absorption in patients taking oral therapy with class 1 antiarrhythmic drugs	Skin erythema, rash	1-3 patches every 12 h	3 patches every 12 h	Patch must be applied to painful area
Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, desipramine)	Metabolism by CYP450 2D6 (note: rapid v. slow metabolizers), potentiates other sedatives	Cardiac conduction block, orthostatic hypotension, sedation, confusion, urinary retention, dry mouth, constipation, weight gain	10-25 mg/d, at bedtime or in divided doses every 12 h; increase dose weekly by 10-25 mg/d	50-150 mg/d; median 50-75 mg/d	More adverse effects with amitriptyline and imipramine; contraindicated in patients with glaucoma and those taking MAOIs
SNRIs					
Duloxetine	Metabolism by CYP450 2D6	Sedation, ataxia, nausea, dry mouth, constipation, hyperhidrosis, anorexia	60 mg once daily; 60 mg every 12 h also safe and effective	60 mg/d (maximum 120 mg/d)	Contraindicated in patients with glaucoma and those taking MAOIs; recent US FDA approval for use in diabetic neuropathy
Venlafaxine	Metabolism by CYP450 2D6 and 3A4	Hypertension, ataxia, sedation, insomnia, nausea, hyperhidrosis, dry mouth, constipation, anxiety, anorexia	37.5 mg once daily; increase dose weekly by 37.5 mg/d	150-225 mg/d (maximum 375 mg/d)	Dose adjustment in patients with renal dysfunction; contraindicated in patients taking MAOIs
Anticonvulsants					
Carbamazepine (CBZ)	Metabolism by CYP450 3A4, 1A2 and 2C8; inducer of CYP450 1A2, 2C and 3A	Sedation, ataxia, rash, diplopia, hyponatremia, agranulocytosis, nausea, diarrhea, hepatotoxicity, aplastic anemia, Stevens-Johnson syndrome	100-200 mg/d, in divided doses every 6-8 h; increase dose weekly by 100-200 mg/d	600-1200 mg/d (maximum 1600 mg/d); for trigeminal neuralgia, controlled-release CBZ every 8-12 h, with short-acting CBZ every 4 h for rescue	First-line therapy for trigeminal neuralgia only; contraindicated in patients with porphyria or atrioventricular block and in those taking MAOIs; monitor CBC, liver function test results and blood levels
Gabapentin	Simple antacids reduce bioavailability	Sedation, ataxia, edema, weight gain, diplopia, nystagmus	300-900 mg/d, in divided doses every 8 h; increase dose weekly by 300 mg/d	1200-2400 mg/d (maximum 3600 mg/d)	Dose adjustment in patients with renal dysfunction
Pregabalin	None documented to date	Sedation, ataxia, edema, diplopia, weight gain, dry mouth	50-150 mg/d, in divided doses every 8-12 h; increase dose weekly by 50-150 mg/d	300-600 mg/d (maximum 600 mg/d)	Dose adjustment in patients with renal dysfunction
Opioids					
Tramadol	Metabolism by CYP450 2D4; risk of serotonin syndrome with SSRI co-administration	Respiratory depression, ataxia, sedation, constipation, seizures, nausea, orthostatic hypotension	50 mg/d, in divided doses every 12 h; increase dose weekly by 50 mg/d	200-400 mg/d (maximum 800 mg/d)	Use with caution in patients with epilepsy
Morphine (or alternative opioid with appropriate dose conversion)	Potentiates other sedatives	Respiratory depression, sedation, nausea, constipation, cognitive dysfunction	5-15 mg (short-acting) every 4 h as needed; after 1-2 wk convert to long-acting preparation and continue dose titration as needed	Benefits of daily morphine equivalents > 180 mg/d have not been established	Screen patients for alcohol/substance abuse and consider "opioid contract"; co-administer pre-emptive stool softeners and antiemetics

Note: CYP450 = cytochrome P450 enzyme, MAOI = monoamine oxidase inhibitor, SNRI = mixed serotonin-noradrenaline reuptake inhibitor, FDA = Food and Drug Administration, CBC = complete blood count, SSRI = selective serotonin reuptake inhibitor.
*This is a nonexhaustive list that includes medications recommended in Fig. 3.

tated by the risk of acetaminophen-related hepatotoxicity (i.e., < 4000 mg acetaminophen).

Although supportive evidence is limited, polypharmacy may be helpful. Therefore, in the event of a partial response to any single drug, one could add an alternate drug. If none of the above tried treatments is effective or tolerated, referral to a pain clinic is warranted for consideration of third-line drugs, interventional treatments and pain rehabilitation programs.

Prescribing considerations

Table 2 provides basic information on drugs recommended in Fig. 3. Given the potential for drug interactions,[130] a thorough review of the patient's current medications is warranted before prescribing any drugs for neuropathic pain. Given the potential for overdose toxicity with opioids and tricyclic antidepressants, suicide risk should be evaluated before prescribing. Some patients need reassurance that analgesia with antidepressants and anticonvulsants does not necessarily imply a diagnosis of depression or epilepsy. Because the central nervous system is depressed by most tricyclic antidepressants, anticonvulsants and opioids, gradual drug dose titration over weeks, toward a maximal tolerated dose, allows for accommodation to adverse effects while reaching an effective dose. Because of this need for gradual dose titration, the physician and patient need to recognize that onset of pain relief will be gradual. If possible, nursing resources should be devoted to weekly patient contact to guide dose titration. Since tricyclic antidepressants are rapidly metabolized in some patients, plasma tricyclic antidepressant levels should be measured if no analgesic or adverse effects are observed at maximal doses so as to safely guide further dose increases.[131] In elderly people, drug treatment should be started at the lowest possible dose and be increased very slowly (i.e., longer titration period) to minimize the risk of falling and related trauma.

Conclusion

Neuropathic pain is a devastating chronic condition that generally can be diagnosed by history and findings on physical examination. For some neuropathic pain syndromes, available treatments are tolerable and afford meaningful relief to a considerable proportion of patients. Nevertheless, many patients report intractable and severe pain, and better treatment strategies are desperately needed.[132] The field of neuropathic pain research and treatment is in the early stages of development, with many goals yet to be achieved. In particular, future laboratory, clinical and epidemiologic[3,9] research into pathogenesis,[64,136] treatment[2,18,118,137,138] and prevention[133–135] of neuropathic pain is expected as well as improved dissemination of new information to health professionals and the public. Over the years to come, many upcoming advances are expected in the basic and clinical science of neuropathic pain as well as in the implementation of improved therapies for patients who continue to experience these devastating conditions.

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Regular review

Peripheral neuropathy

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Peripheral neuropathy is common, often distressing, and sometimes disabling or even fatal. The population prevalence is about 2400 per 100 000 (2.4%), rising with age to 8000 per 100 000 (8%).[1] In Europe the commonest cause is diabetes mellitus, which can produce painful neuropathy, disabling foot ulcers, and death from autonomic neuropathy. Leprosy is still prevalent in Africa, India, and South East Asia. This review explains how general practitioners can approach the first level of diagnosis and warn patients about what lies ahead after referral to a specialist.

Summary points

- Peripheral neuropathy can be into divided into acute and chronic forms, symmetrical polyneuropathy, and multiple mononeuropathy
- Acute neuropathies are diagnostic emergencies
- Neuropathy due to diabetes mellitus and alcohol misuse can be diagnosed in primary care
- Neurophysiological tests distinguish axonal from demyelinating neuropathies
- Demyelinating neuropathies are commonly inflammatory and treatable
- Axonal neuropathies have multiple causes
- Generic management includes foot care, ankle supports, and treatment of neuropathic pain

Methods

I searched Medline from January 1991 until September 2001 using the terms "peripheral neuropathy" and "guideline." The search yielded 11 references, including useful guidelines for the diagnosis and management of diabetic peripheral neuropathy,[2] but no guidelines on the diagnosis and management of generic peripheral neuropathy. This article offers a personal approach to the management of generalised peripheral neuropathy from the perspective of a neurologist with a special interest in the topic. The recommendations also take account of reviews published by authorities in peripheral neuropathy (see educational resources) and a recent audit of a Dutch departmental guideline that showed the value of investigating common causes before doing electrophysiological tests.[3]

Diagnosis

Patients with peripheral neuropathy may present with altered sensation, pain, weakness, or autonomic symptoms. The clinical features vary widely and may resemble myelopathy, radiculopathy, muscle disease, or even hyperventilation. Identifying a neuropathy in patients with coexistent problems can therefore be difficult. The symptoms usually begin in the toes before the fingers and spread proximally.

The classic picture of advanced polyneuropathy with distal wasting and weakness, absent tendon reflexes, and glove and stocking sensory loss should be easy to recognise. The clinical features allow acute symmetrical peripheral neuropathy, chronic symmetrical peripheral neuropathy, and multiple mononeuropathy to be distinguished, each with a different differential diagnosis.

Acute symmetrical peripheral neuropathy

Acute symmetrical peripheral neuropathy is rare but important because the commonest cause is Guillain-Barré syndrome, which can be fatal. The table gives other causes. Common early symptoms are distal paraesthesiae and proximal or distal weakness occurring one to two weeks after a respiratory or gastrointestinal infection. Traditionally, the reflexes are absent, but their retention during the first hours of the illness has led many patients to be dismissed as "hysterical." Once a patient loses the ability to walk and develops facial and bulbar weakness the diagnosis becomes obvious. The rapid progression of sensory or motor deficit requires emergency investigation. Patients usually have to be admitted to hospital because of the danger of respiratory failure. Early treatment should stop the pathological process before axonal dysfunction becomes irreversible.

Guillain-Barré syndrome is usually due to acute inflammatory demyelinating polyradiculoneuropathy caused by an autoimmune response directed against the Schwann cells or myelin. Some cases are due to acute axonal neuropathy, in which glycolipid in the axolemma is targeted. In both forms, treatment with intravenous

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immunoglobulin hastens recovery and reduces the long term disability and is more convenient than plasma exchange.[4] A recent trial suggests that combination treatment with steroids is more effective than intravenous immunoglobulin alone, but the full results are awaited.[5]

Multiple mononeuropathy

Acute multiple mononeuropathy is also a neurological emergency because the commonest cause is vasculitis (box 1). Prompt treatment with steroids may prevent further irreversible nerve damage. If multiple mononeuropathy develops in a patient with an established connective tissue disorder (such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, or Churg-Strauss syndrome) it is reasonable to conclude that vasculitis is the cause. Steroids are the main treatment, with cyclophosphamide being added depending on the severity and general medical condition.

Sometimes peripheral neuropathy is the presenting or sole feature of vasculitis. In this case, vasculitis can be diagnosed only by nerve biopsy.[6,7] In addition, recent biopsy studies indicate that diabetic amyotrophy is due to microvasculitis in the lumbosacral plexus. It presents acutely with pain, weakness, and then wasting in one or both quadriceps muscles.[6–8]

Chronic symmetrical peripheral neuropathy

Most peripheral neuropathies are chronic and usually develop over several months. Diagnosis of the underlying cause may require three stages of investigation. Any history of a general medical disorder could be relevant. Patients should always be asked about alcohol consumption, toxin exposure (insecticides, solvents), and drugs. They should also have a full examination, including breasts and genitalia, to exclude underlying carcinoma.

The commonest causes of neuropathy can be identified from the history, examination, and simple stage 1 investigations (box 2). Sometimes the neuropathy is predominantly sensory and subacute with ataxia that is worse in the dark because of loss of large fibre function and postural sensation. This pattern is produced by some drugs (such as cisplatin), an underlying neoplasm, Sjögren's syndrome, or idiopathic sensory neuronopathy. If other members of the family have similar symptoms, pes cavus, or claw toes, the patient may have hereditary motor and sensory neuropathy or Charcot-Marie-Tooth disease, which is usually autosomal dominant. Difficulty with walking in childhood also suggests a hereditary neuropathy. If patients have a clear cause for their neuropathy and a typical clinical picture, treatment—for instance, of diabetes mellitus or alcohol misuse—can be started without further investigation.

Causes of acute severe generalised peripheral neuropathy

Cause	Predominantly motor	Mixed	Predominantly sensory
Guillain-Barré syndrome	+	+	—
Vasculitis	—	+	—
Diabetes mellitus	—	+	+
Drugs*	—	+	+
Porphyria	+	—	—
Diphtheria	—	+	—
Paraneoplastic neuropathy	—	+	+
Acute idiopathic sensory neuronopathy	—	—	+
Critical illness	+	+	—

*For example, nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.

Box 1: Causes of multiple mononeuropathy

Vasculitis
Primary systemic vasculitis:
- Polyarteritis nodosa
- Churg-Strauss syndrome (vasculitis with blood eosinophilia and asthma)

Systemic vasculitis associated with connective tissue diseases:
- Rheumatoid arthritis
- Sjögren's syndrome

Vasculitis confined to peripheral nerves

Other causes
Sarcoidosis
Lymphoma
Carcinoma
Amyloid

Multiple compression palsies
Associated with metabolic or toxic neuropathy
Hereditary neuropathy with liability to pressure palsies

Second stage investigations

If the cause of the neuropathy is not clear from the stage 1 investigations or is atypical, the patient should be referred to a neurologist. The most important stage 2 investigation is neurophysiological testing (figure). About 80% of symmetrical peripheral neuropathies are axonal and are due to gradual dying back of the axons. In the remaining 20% (demyelinating neuropathies) most of the damage is to the myelin, although axonal degeneration often occurs as the disease advances. The other second stage investigations (box 2) are simple outpatient tests for the commonest causes of peripheral neuropathy.

Third stage investigations

The choice of third stage investigation will depend on whether neurophysiological testing has shown the neuropathy to be demyelinating or axonal.

Box 2: Stage 1 and 2 investigations of peripheral neuropathy

Stage 1
Urine—Glucose, protein
Haematology—Full blood count, erythrocyte sedimentation rate, vitamin B-12, folate
Biochemistry—Fasting blood glucose concentration, renal function, liver function, thyroid stimulating hormone

Stage 2
Neurophysiological tests—Assessment of distal and proximal nerve stimulation
Biochemistry—Serum protein electrophoresis, serum angiotensin converting enzyme
Immunology—Antinuclear factor, antiextractable nuclear antigen antibodies (anti-Ro, anti-La), antineutrophil cytoplasmic antigen antibodies
Other—Chest radiography

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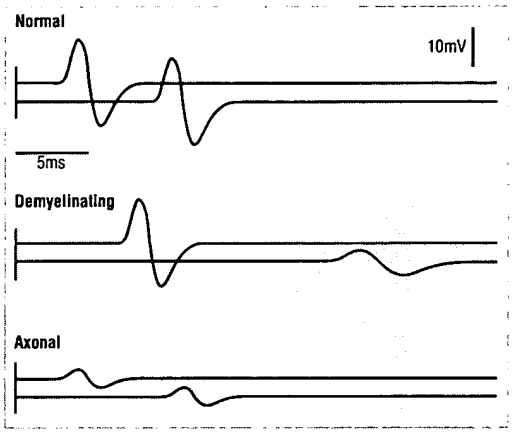

Muscle action potentials after distal and proximal stimulation of a nerve to a muscle such as abductor pollicis brevis. The upper trace of each pair is the record after distal stimulation. In the normal nerve the distal motor latency is short and nerve conduction velocity rapid (>50m/sec). In demyelinating neuropathy the distal motor latency is prolonged and nerve conduction velocity slowed to less than 80% of normal. In axonal neuropathy the action potential is reduced, but the distal motor latency and nerve conduction velocity are unaffected. Multifocal abnormalities with normal conduction velocity suggest multiple mononeuropathy

Demyelinating neuropathy

The causes of demyelinating neuropathy are limited (box 3). If the slowing of nerve conduction affects all nerves roughly equally the diagnosis is likely to be the demyelinating form of Charcot-Marie-Tooth disease (type 1). Seventy per cent of such patients have a duplication of the gene for a 22 kDa peripheral nerve myelin protein on chromosome 17. The duplication causes overexpression of the protein. The clinical picture ranges from classic pes cavus with inverted champagne bottle legs to scarcely detectable clawing of the toes. Different mutations of the same protein and of other myelin proteins cause a similar clinical picture. Genetic counselling and prenatal diagnosis can be offered.

About 10% of patients with a demyelinating neuropathy have a serum paraprotein. Although occasionally associated with a solitary plasmacytoma, the paraprotein is usually benign. The commonest syndrome is a slowly progressive predominantly sensory neuropathy with an IgMκ paraprotein. The paraprotein is an autoantibody directed against the carbohydrate epitopes on myelin associated glycoprotein. The antibody is directly responsible for the neuropathy.

Box 3: Causes of chronic demyelinating neuropathy

- Charcot-Marie-Tooth disease type 1
- Other forms of Charcot-Marie-Tooth disease
- Hereditary liability to pressure palsies
- Other genetic causes—for example, Refsum's disease, metachromatic leucodystrophy
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy
- Paraproteinaemic demyelinating neuropathy:
  - Associated with monoclonal gammopathy of undetermined significance
  - Associated with solitary myeloma

Chronic inflammatory demyelinating polyradiculoneuropathy is the commonest form of acquired demyelinating neuropathy and affects about 2 per 100 000 of the population.[9] The disease is usually predominantly motor, and patients show a proximal as well as distal pattern of weakness; the condition may be relapsing and remitting. Protein concentrations in the cerebrospinal fluid are almost always increased. Chronic inflammatory demyelinating polyradiculoneuropathy is diagnosed by exclusion of the other causes listed in box 3 and from neurophysiological testing, which shows multifocal abnormalities with partial conduction block. This causes the compound muscle action potential following proximal stimulation to be smaller than that following distal stimulation (see figure). It is thought to be an autoimmune disease because of the inflammation in the nerves and response to immunotherapy. There is no diagnostic immunological test, but antibodies to the 28 kDa P0 myelin glycoprotein were identified in about a quarter of cases in a recent series and have been shown to induce experimental demyelination.[10]

Chronic axonal neuropathy

Axonal polyneuropathy can be sensory or sensory and motor. It has many causes, which will often be suggested by the history or examination. The third stage investigations (box 4) should show the less common general medical disorders and identify cases of diabetes mellitus that were not detected by the fasting blood glucose test.[11] Nerve biopsy should usually be done only on patients with distressing neuropathy in whom it might lead to useful treatment.[12] In an audit of 50 cases the biopsy confirmed the diagnosis in 70%, affected management in 60%, and caused persistent pain in 33% of patients.[12] Biopsy should be done in a specialist centre and only when the diagnosis cannot be made in any other way. Specimens are usually taken from the sural nerve under local anaesthetic. Vasculitis is the diagnosis most likely to be found.

After exhaustive investigation no clear cause is found in about 25% of patients. Such chronic idiopathic axonal neuropathy usually occurs in elderly people and is often indolent, predominantly sensory, and length dependent. Patients can be reassured that, although their condition may progress, it will usually do so only slowly and is unlikely to become seriously disabling.[13]

Loss of pain and temperature sensation and spontaneous neuropathic pain, described as burning or pricking, can be prominent symptoms of axonal neuropathy. They are due to degeneration of thinly myelinated and unmyelinated nerve fibres. Occasionally small fibre neuropathy occurs without the thicker myelinated nerve fibres being affected and the nerve conduction test results remain normal. The diagnosis in such cases usually relies on the clinical symptoms and signs alone. Proof of the diagnosis would require skin biopsy or enumeration of unmyelinated nerve fibres in electron micrographs of a nerve biopsy specimen.

Chronic axonal neuropathy occurs in patients with many multisystem hereditary disorders. The diagnosis of these conditions is usually suggested by the other neurological and systemic features. Isolated cases of hereditary neuropathy such as the axonal form of Charcot-Marie-Tooth disease (type 2) can, however, be

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difficult to diagnose.[14 15] In this disease the symptoms usually begin in childhood and are associated with pes cavus and claw toes but may not come to attention until middle or old age. The family history may not be evident without examination of the apparently unaffected relatives. The condition is clinically and genetically heterogeneous, and several gene loci are involved. Molecular genetic tests are available for only a tiny proportion of patients.

Treatment

Any underlying medical cause of peripheral neuropathy, such as diabetes mellitus or vitamin B-12 deficiency, should be treated. Chronic inflammatory demyelinating polyradiculoneuropathy is important to recognise because it is treatable. Corticosteroids are usually used initially as they are the cheapest treatment, but the condition also responds to intravenous immunoglobulin, plasma exchange, and some immunosuppressant drugs.[9] The uncommon variant, multifocal motor neuropathy, responds to intravenous immunoglobulin and possibly immunosuppressant drugs but not to corticosteroids or plasma exchange.[16] Unfortunately, no specific treatment is available for chronic idiopathic axonal polyneuropathy.

Management

Preventive and palliative treatments include foot care, weight reduction, and sensible shoes, boots, or ankle-foot orthoses. Patients with severe leg weakness may need sticks, crutches, or a walking frame. Physiotherapists are best placed to prescribe these aids, which may need to be adapted to take account of weakness of the hands. Simple wrist splints can help weak wrist extension. More complex splints for weak fingers and hands are usually cumbersome and rarely used. Disabled patients require help from a multidisciplinary team including an occupational therapist, who can advise on special utensils and home adaptations. Some drugs help. Sildenafil may correct erectile impotence. In the United Kingdom, the NHS will pay if the neuropathy is due to diabetes mellitus.

Patients with neuropathy may experience pain, which can be severe and out of proportion to any sensory or motor deficit. Painful neuropathy is difficult to treat. The most useful drugs are anticonvulsants, especially gabapentin and carbamazepine, and tricyclic antidepressants, especially amitriptyline. The opioid-like analgesic tramadol has also been shown to be useful in randomised controlled trials.[17]

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Competing interests: RACH is coordinating editor of the Cochrane Neuromuscular Disease Review Group.

Box 4: Stage 3 investigation of peripheral neuropathy

Urine—Bence-Jones protein

Biochemistry—Oral glucose tolerance test

Cerebrospinal fluid—Cells, protein, immunoglobulin oligoclonal bands

Immunology—Anti-HIV antibodies, antineuronal antibodies (Hu, Yo), antigliadin antibodies, serum angiotensin converting enzyme, antiganglioside antibodies, antimyelin associated glycoprotein antibodies

Tests for Sjögren's syndrome—Salivary flow rate, Schirmer's test, Rose Bengal test, labial gland biopsy

Search for carcinoma, lymphoma, or solitary myeloma—Skeletal survey, pelvic ultrasonography, abdominal and chest computed tomography, mammography, or positron emission tomography

Molecular genetic tests—Peripheral nerve myelin protein 22 gene duplication (the commonest cause of Charcot-Marie-Tooth disease type 1) or deletion (hereditary neuropathy with liability to pressure palsies), connexin 32 mutation (X linked Charcot-Marie-Tooth disease), PO gene mutation (another cause of Charcot-Marie-Tooth disease type 1), etc

Additional educational resources

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Patient information

Guillain-Barré Syndrome Support Group (www.gbs.org.uk)
Information and support for people with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and related conditions

Peripheral Neuropathy Trust (www.neuropathy-trust.org)
Information about all forms of neuropathy, especially chronic idiopathic axonal neuropathy

CMT United Kingdom (www.cmt.org.uk)
A site maintained by the UK Charcot-Marie-Tooth disease patient support group

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REPORT

[Report]
Worldwide Peripheral Neuropathy Emerging Market & Product Assessment

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This new EP Publications report:

- Projects the number of patients with key conditions associated with **peripheral neuropathy** in 2007 and 2012
- Reveals vital differences between novel compounds in development to treat **peripheral neuropathy**
- Uncovers the factors and players that will drive the growth of the emerging **peripheral neuropathy** market
- Predicts the commercial potential for current and upcoming drug classes in individual country markets
- Forecasts the value (in USD) of the **peripheral neuropathy** market, by drug class, by condition, and by country, in 2007 and 2012

An Emerging Worldwide Market

Currently, there are no treatments commercially available to effectively prevent reduce, or reverse damage to **peripheral** nerves, or **peripheral neuropathy**. By 2012, there will be over 1.5 million individuals in the seven major pharmaceutical markets ? U.S., France, Germany, Italy, Spain, UK, and Japan

Infection Disease

Mental Disease

Neurodegenerative Disease

Obesity Treatment

OTC Drug

Pain

Pharmaceutical Companies

Prescription Drugs

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who suffer from **peripheral neuropathy** caused from a wide array of factors, including certain major medical conditions (e.g., diabetes, HIV/AIDS) and chemical toxicity (e.g., chemotherapy **treatment** of cancer).

Growing Unmet Need

Peripheral neuropathy is currently managed primarily through controlling the cause of the damage ? for diabetes and HIV/AIDS patients, this represents treating the diseases, while for cancer patients, this means limiting doses of chemotherapy or tolerating significant pain or loss of sensation.

Effective prevention and **treatment** of **peripheral neuropathy** would:

- Improve quality of life for patients with diabetes or HIV/AIDS by providin relief from progressing levels of pain symptoms
- Facilitate full dosing of life-saving chemotherapeutics known to cause **peripheral neuropathy**

Report Objectives & Methodology

In this report, WWMR, Inc., provides an overview of **peripheral neuropathy** in the seven major pharmaeutical markets:

- U.S.
- France
- Germany
- Italy
- Spain
- UK
- Japan

Models representing patient populations and the commercial value (USD) of this emerging market through 2012 are presented in a series of tables, charts, and text commentary describing the important features of the key conditions associated with **peripheral neuropathy**:

- Diabetes
- HIV/AIDS
- Chemotherapy **treatment**

Models and commentary describing the current and future **peripheral neuropathy** market are based on:

- In-depth analysis of the medical literature, including **treatment review** articles, medical textbooks, epidemiological studies, and clinical trials
- Thorough **review** of country-specific and overall trends, as well as country-to-country comparisons, of prescriptions written for specific conditions
- Analysis of drugs in the **peripheral neuropathy** drug pipeline and the future directions in **treatment**
- Interviews with clinicians, including medical directors of selected pain centers and clinicians treating **peripheral neuropathy**

WWMR fs Worldwide **Peripheral Neuropathy** report will allow pharmaceutical and biotechnology executives to:

- Recognize the specific conditions associated with **peripheral neuropath** that have high market potential in the next 10 years
- Understand the type and level of unmet need in the **peripheral neuropathy** market in the US, France, Germany, Italy, Spain, UK, and Japan
- Compare the epidemiology of **peripheral neuropathy** among the 7 major pharmaceutical markets, including projected growth rates
- Target specific patient populations who will benefit most from drugs in th **peripheral neuropathy** pipeline
- Anticipate upcoming competitors and product licensing opportunities
- Recognize the impact of special market dynamics, including potential off-label usage, on product uptake forecasts
- Develop condition- and country-specific forecasts for major conditions associated with **peripheral neuropathy**

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Bandolier

"Evidence based thinking about health care"

Antidepressants for diabetic neuropathy and postherpetic neuralgia

Clinical bottom line

Antidepressants are effective treatments for diabetic neuropathy (NNT 3.4, 95% confidence interval 2.6 to 4.7) and postherpetic neuralgia (NNT 2.1, 1.7 to 3.0) compared with placebo. The NNH for any patient to have a minor adverse effect with antidepressant was 2.7 (2.1 to 3.9) and for a major adverse effect was 17 (10-43).

For over thirty years the management of neuropathic pain has involved the use of both antidepressants and anticonvulsants, but which drug class should be first line choice remains unclear. The dogma that the character of the pain was predictive of the response, burning pain responding to antidepressants and shooting pain to anticonvulsants, was shown to be incorrect in diabetic neuropathy, where patients experiencing both burning and shooting pain responded to tricyclic antidepressants. Most studies on neuropathic pain have involved diabetic neuropathy and postherpetic neuralgia, because these conditions represent the majority of patients with neuropathic pain.

SYSTEMATIC REVIEW

SL Collins et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. Journal of Pain and Symptom Management 2000 20: 449-458.

- *Date review completed: June 1999*

- *Number of trials included: 19*
- *Number of patients: 358 on antidepressant and 278 on placebo (episodes of treatment)*
- *Control group: placebo*
- *Main outcomes: various outcomes equivalent to at least 50% pain relief*

Searching involved numerous electronic databases including MEDLINE, EMBASE, CINAHL, Sigle, PubMed and the Cochrane Library, plus in-house databases of randomised controlled trials in pain. The inclusion criteria used were: full journal publication, adult patients, double-blind design, random allocation to treatment groups which included placebo and either an antidepressant or an anticonvulsant for the treatment of chronic pain due to diabetic neuropathy or postherpetic neuralgia. An adequate description of the original authors' method of clinical diagnosis was required to ensure an accurate diagnosis of the two conditions. For postherpetic neuralgia the pain must have been present for more than three months after zoster eruption to limit the chance of spontaneous cessation of symptoms.

A clinically relevant outcome was defined as a measure equivalent to at least 50% pain relief after the longest reported duration of treatment. This was extracted as dichotomous information from the following hierarchy of outcome measures:

- Top two values on a patient reported 5-point global scale of pain relief or effectiveness or improvement
- Top three values on a patient reported 6-point global scale of pain relief or effectiveness or improvement
- Top value on a patient reported 3-point global scale of pain relief or effectiveness or improvement
- The top two values on a patient reported 4-point categorical pain relief scale 50% or more reduction on a visual analogue scale (VAS) of pain intensity
- A mean score of 6 or less on a 6-item neuropathy scale which included pain and had a maximum possible score of 12.

The majority of studies used a cross-over design and results are presented in terms of patient episodes rather than actual numbers of patients. One patient episode represents the result for one patient completing one part of the cross-over. So for a trial where the patient was crossed-over from placebo to active this would generate two patient episodes.

Adverse effects were classified as minor if reported by a patient who then continued to take the medication and completed the trial. A major adverse effect was one causing the patient to withdraw from the study. Withdrawal due to lack of efficacy was not counted as an adverse effect.

Findings

The studies of antidepressants in diabetic neuropathy and postherpetic neuralgia were small, ranging from 12 to 92 patient episodes in total. Consequently the results of individual trials varied greatly, both in diabetic neuropathy (Figure 1) and postherpetic neuralgia (Figure 2).

Figure 1: Trials of antidepressants versus placebo in diabetic neuropathy

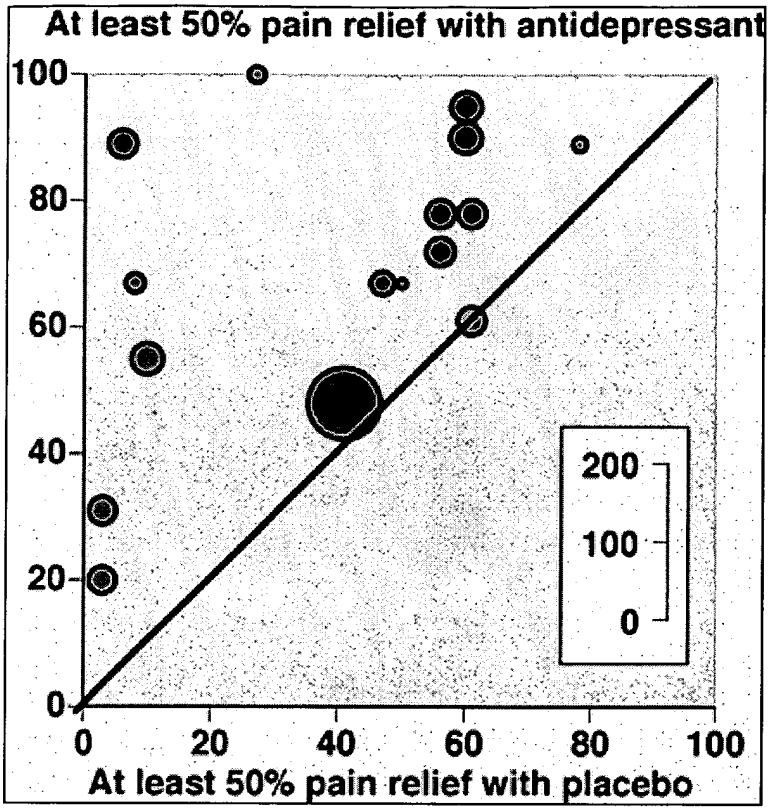
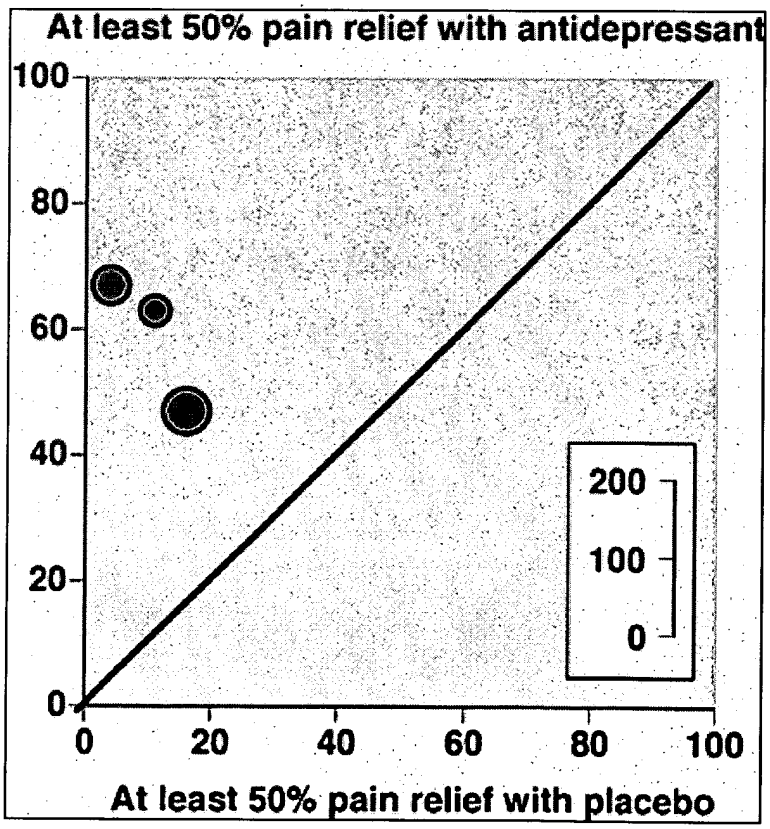


Figure 2: Trials of antidepressants versus placebo in postherpetic neuralgia



Pooled results are shown in Table 1. Over both conditions, 64% of patients had an outcome equivalent to more than 50% pain relief with antidepressant, compared with 30% with placebo. The NNT for at least 50% pain relief compared with placebo was 2.9 (2.4 to 3.7). For every patient who received benefit, one also had a minor adverse effect that did not lead to discontinuation. Nearly 1 patient in 12 discontinued treatment because adverse effects were intolerable, with a NNH of 17 (10-43).

Table 1: Summary results of efficacy and harm for antidepressants in diabetic neuropathy and postherpetic neuralgia

			Number of patien improved or harm number/total (%
	Trials	**Patient episodes**	**Antidepressant**
Efficacy			
Diabetic neuropathy	16	491	185/281 (66%)
Postherpetic neuralgia	3	145	44/77 (57%)
Both conditions	19	636	229/358 (64%)
Harm			
Minor adverse	7	281	114/163 (70%)

effect			
Major adverse effect	16	536	27/325 (8%)

Comment

This review updated previous reviews and confirmed that antidepressants are effective in patients with diabetic neuropathy and postherpetic neuralgia. The degree of benefit, an outcome equivalent to at least 50% pain relief, was valuable, and with an NNT of 3, efficacy was equivalent to that seen in effective analgesics in acute pain (10 mg intramuscular morphine, for instance). Two thirds of patients given antidepressants benefited. For every patient who benefited, one had a minor adverse effect, but continued with the treatment. There were few differences in the efficacy and harm seen with antidepressants and anticonvulsants.

Other reviews on neuropathic pain

It is an interesting observation that rather a lot of reviews (most systematic) have been done around neuropathic pain. It is impossible to abstract them all, and probably unrewarding, in that they cover virtually the same papers. For those readers with a particular interest, a list of those we have found is given below.

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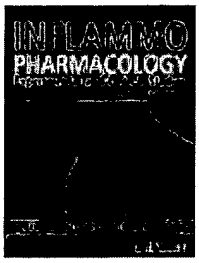

Fluoxetine, a selective serotonin reuptake inhibitor modulates inflammatory and neuropathic pain in the rat

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Abstract The clinical usefulness of classical tricyclic antidepressants has been indicated in a variety of neuropathic pain. The role of selective serotonin reuptake inhibitors (SSRIs) is, however, controversial in pain control. The present study was aimed at evaluating the efficacy of an SSRI, fluoxetine, in neuropathic pain involving peripheral (carrageenan-induced inflammation) and central sensitization (spinal nerve ligation) in rats. Fluoxetine was also assessed for antinociceptive and antiphlogistic effect against acetic acid-induced chemonociception in mice and carrageenan-induced

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inflammation. Fluoxetine (100-400 μg, intraplantar

administration) failed to attenuate either hyperalgesia or cold allodynia in any of the tests employed. Fluoxetine dose dependently increased paw volume in the absence or presence of an inflammatory stimulus which was not reversed by indomethacin (10 mg/kg, p.o). Fluoxetine was ineffective in reducing hyperalgesia and allodynia associated with the rat models. However, fluoxetine dose dependently decreased acetic acid-induced writhings. The results indicated that 5-HT plays a differential role in pain modulation and may not be playing a major role in the maintenance of hyperalgesia and allodynia in the rat models.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS - FLUOXETINE - NEUROPATHIC - INFLAMMATORY PAIN

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News and views

Cortecs Reincarnated

Provalis is the reincarnation of Cortecs. Cortecs was the biotechnology company at the forefront of oral insulin technology in the UK, until it was realised that they had unwittingly licensed-in an oral insulin spiked with glibenclamide (*Lancet* 1991; **338**: 308–309). Provalis has revealed a pre-tax loss of £6.5 million, which is a major improvement on last year's loss of £15.9 million. However, the company recently announced a £10.8 million fully underwritten fundraising at 29.5 p per share to finance the expansion of its Glycosal project. Glycosal is a device for monitoring HbA_{1c}. The company's Chief Executive has said that the company is ready for substantial growth as Glycosal is launched on world markets and new products are acquired and developed. Although Provalis currently intends selling most of Cortecs' drug delivery technologies, they will maintain an interest in oral insulins and hope to gain funding to support trials of Macrulin–an oral insulin product.

Treating Painful Neuropathy

Pain control is a major feature in the management of painful diabetic neuropathy, which is often associated with changes in glycaemic control; and patients with symptoms of shorter duration (< 6 months) should have a better prognosis than those with symptoms for a longer duration (*Clin Diabetes* 2000; **18**:000). Although non-steroidal anti-inflammatory agents such as ibubrofen (600 mg q.i.d.) and sulindac (200 mg b.d.) have shown efficacy, caution is advised due to their association with nephrotoxicity. The tricyclic antidepressants, e.g. amitriptyline, have also relieved pain in patients with diabetic neuropathy, independently of their antidepressant action–showing benefit in both depressed and non-depressed patients. Unfortunately, these agents can cause sedation and confusion and a range of anticholinergic responses–e.g. dry mouth–and are contraindicated in several cardiac conditions and orthostatic hypotension. The antidepressants sertraline and trazodone have been reported to benefit painful neuropathy, but fluoxetine (40 mg/day) did not reduce pain in depressed patients. Nevertheless, in a randomized, double-blind cross-over study, paroxetine (40 mg/day) significantly improved symptoms compared with placebo. However, these serotonin re-uptake inhibitors are not considered as efficacious as the tricyclic antidepressants in the treatment of painful diabetic neuropathy.

The anticonvulsants carbamazepine (200 mg t.i.d.) and gabapentin (900–3600 mg/day) need to be titrated gradually, since side-effects such as somnolence, dizziness and nausea make higher dosages of these drugs difficult to tolerate. However, it has been suggested that lower dosages of gabapentin (≤ 900 mg/day) are ineffective. Other approaches to treatment of painful diabetic neuropathy include the anti-arrhythmic agent mexiletine, the opioid analgesic tramadol, topical application of capsaicin cream, TENS (transcutaneous electrical nerve stimulation) and acupuncture. The latter two methods have been reported to decrease pain in > 75% of patients in uncontrolled studies, but the power of placebo treatment in diabetic neuropathy makes the results of such studies questionable (*Clin Diabetes* 2000; **18**: 000).

More recently, the chance observation that almost total relief from painful neuropathic feet was experienced by a type 2 diabetic patient within 1 week of commencing treatment with the antiobesity agent sibutramine, and recurred upon discontinuing the drug, prompted a small trial. Eight obese type 2 diabetic women (diagnosed 1–29 years) receiving oral antidiabetic medication with a history of painful peripheral neuropathy ranging from a few weeks to 3 years were given 15 mg sibutramine daily. Within about 1 week of starting treatment all patients experienced a 50–100% reduction in pain, but on stopping the medication pain recurred. Since the patients were not participating in a dedicated weight loss programme and compensation for the medication was not available, only two of the patients decided to self-finance

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their treatment with this combined serotonin and noradrenaline re-uptake inhibitor. They reported prompt relief of pain on re-starting the drug. This study highlights the financial importance of enrolling obese patients with neuropathy on a weight loss programme so that they can be treated with sibutramine to enhance weight loss and perhaps of greater importance to the patient, experience sibutramine-associated pain relief (*Diabetes Care* 2000; **23**: 1594)

Spare Tyres and Genes

The association between visceral obesity and the Trp64Arg variant of the β3-adrenoceptor gene remains controversial, although there is mounting evidence for a genetic predisposition for differential accumulation of adipose tissue. To assess the role of the Trp64Arg variant on total and visceral adipose tissue loss, insulin sensitivity and changes in cardiovascular risk factors, 24 obese women aged 57 ± 4 years entered a weight reduction programme for a period of 13 + 3 months. One woman was homozygous for the Trp64Arg variant of the β3-adrenoceptor gene, 10 were heterozygous for this gene variant and the remainder were homozygous normal (*Diabetes* 2000; **49**: 1709–1713). At baseline there were no differences between carriers and non-carriers of the Trp64Arg variant allele for adiposity measurements, glucose disposal and lipid profiles. At the end of the study weight loss, total body fat reduction and improved glucose disposal was similar in both groups, but there was less improvement in total cholesterol : high density lipoprotein (HDL) cholesterol ($p = 0.04$) in carriers compared to non-carriers. Interestingly, carriers of the Trp64Arg variant allele lost 43% less visceral adipose tissue than non-carriers, suggesting that those carrying the Trp64Arg variant allele have an impaired capacity to lose visceral fat under conditions of caloric restriction. It is small consolation for postmenopausal women to blame their genes when, despite fighting the battle of the bulge, their spare tyres remain.

Whole Grain and Stroke: A Female Perspective

Consumption of a high fibre diet is generally accepted as being beneficial. As part of the Nurses Health Study a prospective cohort of 75 521 women aged 38–63 years were followed-up for 12 years and completed food frequency questionnaires in 1984, 1986, 1990 and 1994. On entering the study the women did not have a history of diabetes, coronary heart disease, stroke or other cardiovascular disorders, but during the 861 900 person years of follow-up 352 cases of ischaemic stroke had occurred. An inverse relationship between whole grain consumption and ischaemic stroke risk was observed, and this association remained essentially unchanged even when adjustments were made for known cardiovascular risk factors such as saturated fat consumption, smoking and lack of exercise. Although a higher intake of whole grain (unrefined) foods was associated with a lower risk of ischaemic stroke amongst women, independent of known cardiovascular risk factors, it is noteworthy that no significant association was observed between total grain intake and risk of ischaemic stroke (*JAMA* 2000; **284**: 1534–1540).

A Pill For Gestational Diabetes?

Whilst the cynics sometimes suggest that diagnosis and treatment of gestational diabetes merely increases the expense and complexity of perinatal care, the majority of clinicians consider that moderate carbohydrate abnormalities associated with pregnancy require attention. Maternal hyperglycae-

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mia is the commonest cause of foetal hyperinsulinaemia and consequent foetal macrosomia. Foetal death, generally associated with foetal macrosomia in late pregnancy, has long been recognised as an ever-present risk in women with pre-existing diabetes, but for many years these late deaths were ascribed to hypoxaemia. However, studies in sheep demonstrated that foetal hypoxaemia was a direct result of foetal hyperinsulinaemia. The foetal hyperinsulinaemia increased the uptake of oxygen from the foetal circulation at a greater rate than the placenta could supply it, resulting in foetal hypoxaemia. Thus, to reduce the risk of foetal macrosomia it is now considered important to minimise maternal hyperglycaemia by intensive insulin treatment throughout pregnancy (*New Engl J Med* 2000; **343**: 1178–1179).

A recent study in 98 Caucasian women with type 1 diabetes monitored glycaemic control before the 12th week of gestation to term, and grouped the women according to their average daily glucose concentrations during the second and third trimester. Mothers who achieved an average daily glucose concentration of < 95 mg/dl (≈ 5.3 mmol/l) throughout the second and third trimesters gave birth to infants similar in weight and other anthropometric parameters to infants of non-diabetic mothers. However diabetic mothers whose glycaemic control averaged > 95 mg/dl for the second and < 95 mg/dl for the third or > 95 mg/dl for both trimesters gave birth to large-for-age babies with altered anthropometric parameters. Thus, it is highly beneficial to maintain maternal daily glucose values < 95 mg/dl throughout pregnancy, regardless of maternal diabetic aetiology (*Diabetes Care* 2000; **23**: 1494–1498.)

Gestational diabetes, which generally presents in the second or third trimester of pregnancy, is treated with insulin if diet and exercise fail to achieve adequate glycaemic control. Oral hypoglycaemic agents have not been used during pregnancy for fear of teratogenicity, despite organogenesis occurring in the first trimester. The babies of pregnant women taking first generation sulphonylureas often experienced prolonged hyperinsulinaemic hypoglycaemia, and fears that transplacental passage of sulphonylureas and excess glucose would further stimulate foetal insulin secretion and foetal growth have led to insulin being the medication of choice (*New Engl J Med* 2000; **343**: 1178–1179).

In a recent study 404 women with gestational diabetes were randomly assigned to receive insulin or glyburide between weeks 11 and 33 of gestation. It was necessary to transfer eight women (4%) from glyburide to insulin therapy to achieve adequate glycaemic control. Throughout the treatment period glycaemic control was similar in both groups and there were no significant differences in pregnancy outcome. (For glyburide and insulin therapy, respectively, the incidence of large-for-age babies was 12% and 13%; birth weight > 4000 g was 7% and 4%; lung complications was 8% and 6%; hypoglycaemia was 9% and 6%; foetal abnormalities 2% and 2%). Glyburide was not detected in cord serum and insulin concentrations were similar in both groups. This study suggests that glyburide is an effective alternative to insulin for the treatment of gestational diabetes (*New Engl J Med* 2000; **343**: 1134–1138). Although compliance is not generally an issue during pregnancy, some patients would find pills preferable to injections.

Metformin, Diet and Polycystic Ovary Syndrome

Body weight, fat distribution, glucose metabolism and sex hormones were assessed in 20 overweight (BMI > 28 kg/m^2) women with polycystic ovary syndrome (PCOS) and a control group without PCOS, but similar in age and body fat distribution. All subjects were given a hypocaloric diet (1200–1400 kcal/day) for 1 month before randomization to additional treatment with metformin (850 mg twice daily) or placebo for 6 months (*J Clin Endocrinol Metab* 2000; **85**: 2767–2774). All women treated with metformin lost significantly more weight, experienced decreased leptin concentrations and significant reductions in glucose-stimulated insulin secretion compared with women treated with placebo. In addition, metformin therapy improved hirsutism and menstrual regularity and decreased testosterone concentrations in women with PCOS. Weight loss was associated with decreased fasting insulin concentrations in all subjects, but FSH, LH, DHEA and progesterone were not altered. Metformin, however, is associated with

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reduced vitamin B12 absorption in 10–30% of patients, but recently oral calcium supplementation has been shown to reverse this effect (*Diabetes Care* 2000; **23**: 1227–1231).

Weight Loss: Something To Die For?

The majority of people with type 2 diabetes are overweight or obese at diagnosis and it is standard practice to encourage weight loss in these individuals. It is generally accepted that weight loss will improve insulin sensitivity and other parameters influencing glycaemic control, although it has been suggested that insulin resistance tends to plateau at a BMI of around 35 kg/m^2. There is debate about whether glycaemic control improves due to reduced weight and the associated reduction in insulin resistance, or whether the improvement is due to restricted food intake reducing total calorie intake and carbohydrate flux (*Diabetes Care* 2000; **23**: 1451). When eight obese (BMI 36 + 3 kg/m^2) type 2 diabetic patients were hospitalised for 25 days and given a eucaloric diet followed for 10 days each by a diet supplying 25% and then 75% of calorie requirements, the patients lost 2–10 kg of body fat. Each dietary regimen improved fasting plasma glucose concentrations ($p < 0.05$) compared with baseline, endogenous glucose production was also reduced ($p < 0.05$), due entirely to a decrease in glycogenolysis whilst gluconeogenesis remained constant. However, within 10 days of relaxing energy restriction endogenous glucose production and glycogenolysis had returned to baseline. Interestingly, blood glucose clearance rate had increased by day 20 ($p < 0.05$) of the study, and this partially preserved glycaemic improvements despite the return to baseline of endogenous glucose production. The high baseline rates of fat oxidation and lipolysis were maintained throughout the study, which contrasts with the increases observed upon energy restriction in non-diabetic individuals (*Diabetes* 2000; **49**: 1691–1699).

Although weight loss is generally considered beneficial in reducing morbidity there is little evidence that it increases longevity in people with type 2 diabetes. Review of the literature to date may be considered equivocal in terms of mortality, possibly because studies fail to differentiate between intentional and unintentional weight loss, since the latter may be due to disease factors such as unrecognised malignancies. A recent prospective analysis, with a 12-year follow-up (1959–1972), of 4970 overweight diabetic patients, mean age of 55 years, showed that those reporting intentional weight loss experienced 25% lower total mortality than those not reporting intentional weight loss. An average weight loss of 24 lb (10.9 kg; ≈ 11% of initial body weight) was recorded in this study and a 20–29lb intentional weight loss was associated with the largest reduction (33%) in mortality, whereas a > 70 lb (31.82 kg) weight loss was associated with a small increase in mortality. The data presented in this observational study do not address this small increase in mortality so one is not even left with food for thought (*Diabetes Care* 2000; **23**: 1499–1504).

...And Diabetic Indigestion Sir?

It is estimated that gastroparesis may affect as many as 75% of people with diabetes, causing digestive disturbances such as 'indigestion', loss of appetite, bloating and vomiting. The delayed gastric emptying can cause difficulties when taking medication, particularly drugs designed to exert effects coincident with meal digestion. A recent study in diabetic mice showed that delayed gastric emptying was remedied by administration of sildenafil (Viagra) (*J Clin Invest* 2000; **106**: 373–384). Sildenafil has also been of benefit in the treatment of primary pulmonary hypertension, when it is thought to act as a selective pulmonary vasodilator by preferentially inhibiting cGMP-specific phosphodiesterases (*New Engl J Med* 2000; **343**: 000), raising the possibility that this anti-impo-

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tence drug has additional benefits. If these observations lead to new clinical usage, sildenfil could conceivably become a prescription drug with an action which, depending upon your opinion, could simultaneously be labelled a desired side-effect or an adverse event.

Islet Expression of PPARγ

A few years ago peroxisome proliferator-activated receptors (PPARs) were not prominent contibutors to the diabetes and metabolism scene. This family of at least three nuclear receptors (α, δ and γ) has established roles in adipogenesis, lipid catabolism and hepatic peroxisome proliferation (*Br J Pharmacol* 2000; **129**: 823–824). However, since the clinical advent of the thiazolidinedione (TZD) class of oral antidiabetic agents PPARs have moved to centre stage with PPARγ commanding a lead role as the star of the TZD glucose-lowering mechanism. TZD stimulation of PPARγ offered a new mechanistic approach to the treatment of insulin resistant type 2 diabetes, by acting mainly to reduce peripheral insulin resistance. This provides a somewhat different style to the long-established biguanide, metformin, which acts more to reduce hepatic insulin resistance and thereby decrease hepatic gluconeogenesis.

Celebrities need to be multifaceted to maintain our interest, and ppARg is no exception. Pre-clinical studies, *in vivo* and *in vitro*, have demonstrated an improvement in pancreatic islet morphology and β-cell function, suggesting an effect of TZDs on the endocrine pancreas (*Diabetes* 1998; **47**: 1326–1334; *J Biol Chem* 1998; **273**: 3547–3550). PPARγ has now been isolated from the pancreata of brain-dead, non-obese, non-diabetic adult donors. The islet expression of PPARγ was about two-thirds of that found in mesenteric white adipose tissue, and this receptor was evident in α, β and δ cells (*Diabetologia* 2000; **43**: 1165–1169). PPARγ mRNA was detected in all subjects studied, but there were marked differences in expression highlighting the scope for individual variation in response to PPARγ agonists such as TZDs. This observation raises the prospect of PPARγ agonists influencing glucose homeostasis by exerting a direct effect on the pancreatic β-cell.

Absolutely Flab-u-less

When the conventional approaches of diet and exercise fail to fight the flab and drug treatments are similarly feeble at shifting the fat, there is the opportunity for adipose tissue to disappear from a mere suck of a surgeon's vacuum. Liposuction is increasing in popularity amongst those who have the desire and wealth to acquire taut designer contours and is being considered as a medical method of reducing abdominal adiposity. However, little attention has been paid to the possible adverse effects of this 'quick fix' method of getting into shape although according to the American Society for Aesthetic Plastic Surgery 287 000 procedures were undertaken in the USA in 1999.

There are several different liposuction techniques–which may be broadly considered as 'dry', 'wet' and 'tumescent'–which essentially involve inserting a cannula into the fatty area to be removed, breaking down the cells and applying suction. The 'dry' technique is rarely used, and the currently popular 'wet' techniques require the area to be flushed with anaesthetic (e.g. lidocaine), saline and epinephrine (to constrict local blood vessels and reduce bleeding). During a 'wet' procedure 6–8 oz of fluid would be injected regardless of volume of tissue for subsequent removal, whereas a 'super wet' procedure which is usually performed under epidural or general anaesthetic introduces 1 ml of solution for each ml of aspirate since this approach ideally reduces blood loss. The 'tumescent' technique injects five times as much fluid as aspirate under the influence of local anaesthetic. Some practitioners are adding ultrasound to a wet procedure in order to break the adipocytes more efficiently, raising the possibility of tissue death due to high temperatures if the wand is not constantly moving (*FDA Consumer* 2000; **24**: 000).

Although very few adverse liposuction reports are reaching the Food and Drug Administration (FDA) via the formal reporting channels, the American Society of Plastic Surgeons has announced a

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death rate of one in 5000 for procedures undertaken between 1994 and 1998–a higher toll than from traffic accidents. Most liposuction procedures are undertaken in offices and the lack of FDA reporting may be due to a system which does not require reporting of adverse events from office procedures. Even if the patient is subsequently hospitalized, reporting is not mandatory. Following liposuction, patients may need nursing care for several days to support rehydration, compression bandaging and pain control. Adverse events associated with liposuction include surgical shock, haemodilution and fluid overload, particularly in patients losing a lot of fat, e.g. 11 lb (5 kg), toxic shock, necrotizing fasciitis, cardiac dysrhythmias, oedema, nerve compression and burns following ultrasound. Additionally excess lidocaine can result in cardiac complications, brain agitation leading to seizure and coma, particularly in patients with poor hepatic clearance.

Liposuction can also be disappointing in that patients may be left with wavy or uneven skin and fluid pockets–where more than adipose tissue has been removed–and fat is subsequently deposited elsewhere and can appear more unsightly than fat deposited where nature originally intended. Nevertheless, there have been reports of improvements in cardiovascular risk profile following large volume (10 lb/4.5 kg) liposuction from the abdomen, hips and chest. Such reports have prompted the inclusion of a study in the DPT-2 (Diabetes Prevention Trial–type 2) to investigate the physiological effects and compensatory metabolic changes resulting from removal of subcutaneous fat by liposuction. The study, which started in August 2000, is recruiting 20 women (10 of whom will be of African-American descent), aged 18–50 years who are 30–50 lb (13.6–22.7 kg) overweight, have increased insulin concentrations or abnormal glucose tolerance. They will be followed-up for 12 months after surgery.

Breathe In-sulin

To assess the metabolic effect and the variability of responses elicited by inhalation of 87.2 U insulin powder combined with an absorption enhancer, 13 healthy men received insulin on separate study days and responses were measured using a euglycaemic glucose clamp at 5 mmol/l over an 8-h period after administration. On one occasion subjects received an i.v. dose of 5.5 U regular insulin, on another they received 10.2 U regular insulin s.c. and inhaled insulin was administered on three occasions (*Diabetes Care* 2000; **23**: 1343–1347). The onset of action of inhaled insulin and time of maximal action occurred sooner ($p < 0.0001$), and after 2 h the metabolic effect was greater ($p < 0.0001$), than following s.c. insulin administration, but maximal glucose infusion rate and total metabolic effect were similar for both methods of delivery. This study concluded that the intra-individual variability of metabolic effects following inhaled insulin with an absorption enhancer was comparable to that of insulin administered subcutaneously.

Yin, Yang, Cinnamon

Media attempts to discredit modern Western medical practices have fuelled the alternative remedy market and a burgeoning industry is being built on anecdotal accounts of benefits, without recognised validation, that the fêted treatment is either safe or efficacious. Integrative medicine is the title ascribed to combining conventional and alternative medicine and to assist this approach the National Integrative Medicine Council (NIMC) has been formed in Tuscon, Arizona, to aid collaboration between conventional and alternative medicine.

More than 1000 plants have been reported as treatments for diabetes, but few have been adequately scrutinized (*Act Chim Ther* 2000; **26**: 131–150). However, cinnamon appears to have caught the media imagination. Cinnamon is a traditional treatment for diabetes on the Indian subcontinent and studies have shown that consumption of powdered cinnamon for a month decreased fasting plasma glucose and improved glucose tolerance in diabetic patients. Increased insulin secretion was also observed 30 min after consumption of 20 g of cinnamon (Second World Congress on Diabetes in the Tropics and Developing World, 1981, Abstract 80). More recently, an insulin secretory

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action of cinnamon was observed in isolated islets (*Horm Res* 1992; **37**: 225–229) and the same investigators have also shown that bioactive cinnamon compounds affect protein phosphorylation-dephosphorylation reactions in rat epididymal adipocytes upstream of PI3′-kinase. These observations suggest that cinnamon extracts may be of benefit in treating insulin resistance (*Horm Res* 1998; **50**: 177–182).

American ginseng has also been in the news following studies showing that this traditional Oriental remedy for diverse ailments, including diabetes, reduced hyperglycaemia in type 2 diabetic patients following a 25-g oral glucose challenge (*Arch Intern Med* 2000; **160**: 1009–1013). Interestingly, 3–9 g of ground ginseng root administered up to 2 h before the glucose challenge effectively reduced the hyperglycaemic response (*Diabetes Care* 2000; **23**: 1221–1226). Various species of ginseng have been investigated and several antidiabetic compounds have been identified. Japanese scientists have worked extensively on ginseng, including American ginseng, and several hypoglycaemic polysaccharides have been identified and patented (*J Nat Prod* 1987; **50**: 188–190). What goes around comes around!

Bye Bye Humulin

In September Eli Lilly announced that over the next 6 months it would be withdrawing some of its 'human' insulins, namely Humulin M1 (10/90 mixture) and Humulin M4 (40/60 mixture). The Humulin M5 (50/50 mixture) for pen injector devices will also be phased out and the Humulin 1.5-ml cartridges are to be discontinued. Many people will need to transfer to the larger 3-ml pens, which may be more difficult for children to handle and cause problems for people with poor manual dexterity. It is also of note that many patients will not have used all the insulin in the larger cartridge within its 28-day use-by limit. It is estimated that at least 60 000 people could be directly affected by this Eli Lilly decision.

STRIP: Prevent the Rot Setting In

Autopsies of American casualties during the Korean and Vietnam wars revealed the blood vessels of old men in the bodies of hitherto fit, healthy young men and sounded the alarm bells that cardiovascular risk factors were evident early in life. More recently 760 autopsies were carried out on 15–34-year-old victims of murder, accident and suicide. Assessments made in accordance with the American Heart Association's guidelines showed that 2% of 15–19-year-olds and 20% of 30–34-year-old men had advanced coronary artery lesions, compared with 8% of 30–34-year-old women. Atherosclerotic stenosis was also more prevalent in older men (19%) than women (8%). Risk factors (smoking, dyslipidaemia, hypertension, impaired glucose tolerance and obesity) were considered and it was noted that less advanced lesions were associated with higher high density lipoprotein (HDL) cholesterol whilst advanced lesions were associated with obesity (BMI > 30) (*Circulation* 2000; **102**: 374–379).

Although there is mounting evidence that children with high serum cholesterol are predisposed to developing coronary heart disease there is concern that restriction of dietary fat intake early in life may have detrimental effects on normal growth and development. The Special Turku Coronary Risk Factor Intervention Project (STRIP) is a prospective randomised trial aimed at decreasing exposure to known environmental atherosclerosis risk factors (*JAMA* 2000; **284**: 993–1000). As part of this project babies were recruited at 7 months of age and assigned to a reduced fat or normal diet. Serum lipids were monitored at 7, 13 and 24 months and at yearly intervals thereafter until 5 years of age when a neurological assessment was also performed. Restricting dietary fat intake to 30–35% of energy at a ratio of 1 : 1 : 1 (saturated : monounsaturated : polyunsaturated) with a maximum intake of 200 mg/dl cholesterol resulted in these children consistently having serum cholesterol concentrations 3–5% lower than those of children who had received 'normal' diets. This reduction in dietary fat intake did not negatively affect neurological development.

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WOSCOPS and Lipid

Factors predictive for development of glucose intolerance and diabetes are unclear, therefore the West of Scotland Coronary Prevention Study (WOSCOPS) aimed to establish baseline predictors (*Diabetologia* 2000; **43**(Suppl); Abstract 286). In this group of 5949 men, of whom 192 developed glucose intolerance, baseline BMI, glucose, triglycerides and white cell count were significant predictors for the development of glucose intolerance. Interestingly pravastatin treatment reduced the risk of developing glucose intolerance, possibly due to its lipid lowering effects or its more recently noted anti-inflammatory actions. Recently the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial has reported that treatment with pravastatin (40 mg/day) had a moderate effect on reducing the risk of stroke from any cause. Although treatment reduced the risk of non-haemorrhagic stroke no effect was noted on the incidence of haemorrhagic stroke (*New Engl J Med* 2000; **343**: 317–326).

Actos Arrives In Europe

The thiazolidinedione pioglitazone (Actos) received European Marketing authorisation in October 2000, and this was closely followed by its UK launch in November 2000. Pioglitazone has been approved for use in combination with a sulphonylurea or metformin in patients who are not adequately controlled on either therapy alone. This drug is available as 15 mg or 30 mg tablets and medication need only be taken once daily, with or without food. In 1999 pioglitazone entered the USA, where more than 900 000 patients were using the drug within its first 18 months on the market. Thiazolidinedione troglitazine (Rezulin/Romozin) was associated with idiosyncratic hepatoxicity, therefore it is now a precautionary measure to assess liver enzymes before commencing treatment with a thiazolidinedione, and pioglitizone (Actos) therapy should not be started if liver enzymes are elevated ($> 2.5 \times$ ULN). During the first 12 months of pioglitazone treatment liver enzymes should be monitored every 2 months and periodically thereafter and the drug should be discontinued if there are symptoms of hepatic impairment or ALT$>3 \times$ ULN. Patients with hepatic impairment are contraindicated for treatment with pioglitazone, as are patients who have been diagnosed or have a history of cardiac failure. It is noteworthy that in Europe, unlike the USA, pioglitazone has not been approved for monotherapy or in combination with insulin.

Buddy, Can You Spare A Dime?

In the autumn the American Diabetes Association sent a letter to President Clinton highlighting the need for greater funding for diabetes research, citing that proposed funding levels at the National Institutes of Health (NIH) would be 40% lower than recommended by the Congressionally established Diabetes Research Working Group (DRWG), and that funding for the Centers for Disease Control (CDC) would be 50% lower than experts recommend. It was noted that in proportion to the total NIH budget, that allocated to diabetes research has dropped by 30% since 1981, yet the DRWG has recognised the impact of diabetes, which now affects 6–7% of the US population and accounts for at least 10% of all healthcare expenditure. The number of diabetic Americans has increased by nearly 700% in the last 40 years, and a further 30% increase by 2025 has been predicted. However, between 1990 and 1998 diabetes increased by >30%. Alarmingly, during the 1990s the incidence of diagnosed diabetes has increased by 40% and 50% among people in their 40s and 30s, respectively, and type 2 diabetes is a newly-emerging disease amongst children and adolescents. Annual healthcare coverage for people with diabetes is currently 3–4 times more expensive than for healthy people and as the earlier onset of diabetes increases the prospect of earlier onset of diabetic complications there will be attendant personal, social and economic ramifications. Finally, according to the DRWG 'the next decade offers important research opportunities that, if seized now, can vastly improve the lives of people with or at risk for diabetes.' Please, Mr President .....

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....And Finally Some Interesting Snippets

• Dr Charles Brooke Flint Gibbs died in August at the age of 105. In 1940 he was amongst the 32 founding members of the American Diabetes Association–an organisation which now has > 280 000 members. He was the last surviving founding member and the oldest living alumni of Syracruse University College of Medicine. He was highly regarded for his dedication to diabetes and only retired from active practice 20 years ago.

• The UK Department of Health has announced that hospital consultants can prescribe insulin pumps as part of the National Health Service treatment of diabetic patients. However, this opportunity is dependent upon local health authority allocation of resources.

• The US postal service unveiled a Diabetes Awareness Commemorative stamp at the end of October to mark the start of its year-long diabetes awareness campaign. The campaign is being mounted in association with several agencies including the Juvenile Diabetes Foundation, the American Diabetes Association, the National Institutes of Health and Centers for Disease Control and Prevention.

• In September 2000 Brazil became the first South American country to receive the prandial insulin releaser nateglinide (Starlix). Nateglinide has been available in Japan since August 1999 and it is anticipated that this Novartis product will reach the North American and European marketplace within the next 12 months.

• The Mount Sinai Institute, New York, lectures on diabetes and obesity are reviewed in *Diabetes Care* 2000, **23**: 1584–1590.

• Between 1990 and 1998 the prevalence of diabetes in the USA rose from 4.9% to 6.5%–an increase of 33%. The prevalence of diabetes was highly correlated with the prevalence of obesity (*Diabetes Care* 2000; **23**: 1278–1283).

• Between 1998 and 1999 obesity increased by 6% in the USA (*JAMA* 2000; **284**: 1650–1651).

• According to the American Obesity Association obesity costs society about $100 billion a year and is responsible for almost as many preventable deaths as smoking (300 000).

• A survey of 2630 English children showed that the frequency of overweight ranged from 22% at 6 years of age to 31% at 15 years, with obesity at these ages ranging from 10% to 17%, respectively (*Lancet* 1999; **354**: 1874–1875).

• The antiobesity agent sibutramine has been given a favourable opinion by the European CMCP.

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These search terms have been highlighted: **peripheral neuropathy treatment differs**

Peripheral Neuropathy

Peripheral neuropathy is a common neurological disorder resulting from damage to the **peripheral** nerves. It may be caused by diseases of the nerves or as the result of systemic illnesses.

Many neuropathies have well-defined causes such as diabetes, uremia, or nutritional deficiencies. In fact, diabetes is one of the most common causes of **peripheral neuropathy**.

Other causes include mechanical pressure such as compression or entrapment, direct trauma, penetrating injuries, contusions, fracture or dislocated bones; pressure involving the superficial nerves (ulna, radial, or peroneal) which can result from prolonged use of crutches or staying in one position for too long, or from a tumor; intraneural hemorrhage; exposure to cold or radiation; and vascular or collagen disorders such as atherosclerosis, systemic lupus erythematosus, scleroderma, sarcoidosis, rheumatoid arthritis, and polyarteritis nodosa.

A common example of entrapment **neuropathy** is carpal tunnel syndrome, which has become more common because of the increasing use of computers. Although

the causes of **peripheral neuropathy** are diverse, they produce common symptoms including weakness, numbness, paresthesia (abnormal sensations such as burning, tickling, pricking or tingling) and pain in the arms, hands, legs and/or feet. A large number of cases are of unknown cause.

Therapy for **peripheral neuropathy differs** depending on the cause. For example, therapy for **peripheral neuropathy** caused by diabetes involves control of the diabetes. In cases where a tumor or ruptured disc is the cause, therapy may involve surgery to remove the tumor or to repair the ruptured disc. In entrapment or compression **neuropathy treatment** may consist of splinting or surgical decompression of the ulnar or median nerves. Peroneal and radial compression neuropathies may require avoidance of pressure. Physical therapy and/or splints may be useful in preventing contractures (a condition in which shortened muscles around joints cause abnormal and sometimes painful positioning of the joints).

Recovery from **peripheral neuropathy** is usually slow. Depending on the type of **peripheral neuropathy**, the patient may fully recover without residual effects or may partially recover and have sensory, motor, and vasomotor (blood vessel) deficits. If severely affected, the patient may develop chronic muscular atrophy.

Information provided by the
National Institute of Neurological Disorders and Stroke,
National Institutes of Health

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Each year, Medical College of Wisconsin physicians care for more than 180,000 patients, representing nearly 500,000 patient visits. Medical College physicians practice at Children's Hospital of Wisconsin, Froedtert Memorial Lutheran Hospital, the Milwaukee VA Medical Center, and many other hospitals and clinics in Milwaukee and southeastern Wisconsin.

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